# The American Journal of Medicine



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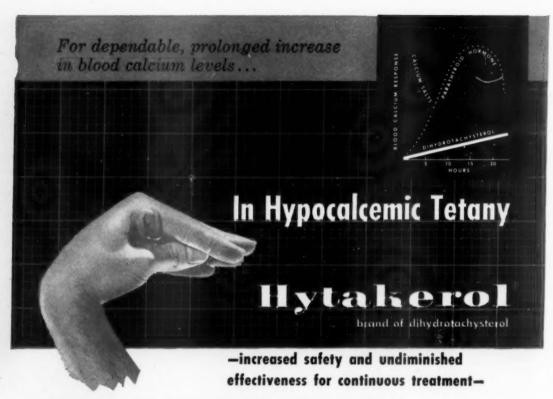
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- Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
- Sandock, Isadore: Tetany and ovarian function. J.A.M.A., 160:659, Feb. 25, 1956.

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# The American Journal of Medicine

Vol. XXIV MARCH, 1958 No. 3

# CONTENTS

# Editorial

The Specificity Hypotheses of Psychosomatic Medicine. Koch's Postulates Revisited
S. Howard Armstrong, Jr. 323

# Clinical Studies

The Natural History of Postnecrotic Cirrhosis. A Study of 221 Autopsy Cases
RICHARD A. MACDONALD AND G. KENNETH MALLORY 334

This detailed analysis of the clinical, laboratory and pathologic characteristics of 221 cases of postnecrotic cirrhosis brings out several points of interest. It would appear that there has been a substantial increase in the incidence of this form of cirrhosis in the past decade. This presumably is
related to the increased incidence of viral hepatitis, both orally and parenterally transmitted, although apparently usually at a subclinical level since only one-fourth of the patients gave a history
of antecedent jaundice, and this often many years before. The incidence of primary hepatic carcinoma was unexpectedly high (14 per cent), indeed higher than with Laennec's cirrhosis. Demise
resulted more frequently from intercurrent infection and portal hypertension with gastrointestinal
hemorrhage than from hepatic failure. These and other interesting (and sometimes unanticipated)
findings emphasize the changing picture of postnecrotic cirrhosis, as herein defined.

### Circulatory Changes in Chronic Liver Disease

JOHN F. MURRAY, A. M. DAWSON AND SHEILA SHERLOCK 358

This paper admirably ties together a number of loose ends, each in itself long puzzling, relating to the effects of chronic liver disease on the circulatory dynamics. The association of increased cardiac output with portal cirrhosis, in a substantial proportion of cases, is confirmed; significantly, the cardiac index remains within normal limits in patients with biliary cirrhosis or extrahepatic portal vein obstruction. The implications of this circulatory abnormality are discussed. The significance of increased plasma volume and of low arterial oxygen saturation, occasionally encountered in patients with portal cirrhosis, also is considered, and the possibility of shunting of blood through pulmonary arteriovenous anastomoses discussed in some detail. Of added interest are the authors' remarks concerning possible relationships between these circulatory derangements and the appearance of clubbing of the fingers and of spider angiomata. There is much food for thought in this illuminating study.

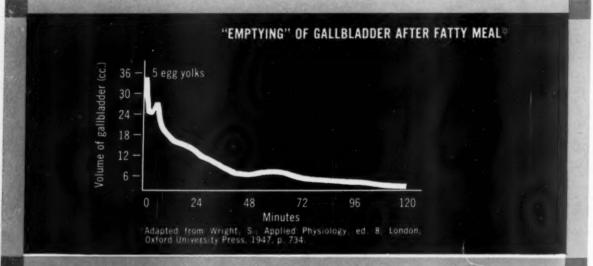
# The Problem of Increasing Azotemia During Management of Diabetic Acidosis ROBERT W. TREVER AND LEIGHTON E. CLUFF

A discussion of the manifold causes, not always clearly definable, of azotemia in patients with diabetic acidosis, with an account of three particularly obscure cases.

Contents continued on page 5

# AN AMES CLINIQUICK

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# What's wrong with the term "emptying of the gallbladder"?

The gallbladder discharges bile by fractional evacuation. It is not emptied completely at any one time even following a fatty meal.

Source-Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, vol. 2, p. 1177.

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The Fluid and Electrolyte Therapy of Severe Diabetic Acidosis and Ketosis. A Study of Twenty-nine Episodes (Twenty-six Patients)

HELEN EASTMAN MARTIN, KENDRICK SMITH AND MARY LU WILSON 376

This study is another attempt to work out a general plan of water and electrolyte replacement in the treatment of severe ketoacidosis. In respect to osmolarity of the serum, the prevalence of hyperosmolarity in patients upon hospital admission indicates the predominant need for water. The requirements for sodium, potassium, chloride, bicarbonate and phosphate are then successively considered and average intakes are suggested for the early, more acute phases of management. The authors find that these requirements can best be met by infusion of 2 to 3 L. of combined M/6 sodium lactate and 0.9 per cent saline solution, followed by 3 to 4 L. of Butler's solution, with such additional potassium and phosphate supplements as are indicated in individual cases.

Progression of Amaurotic Family Idiocy As Reflected by Serum and Cerebrospinal Fluid Changes

STANLEY M. ARONSON, ABRAHAM SAIFER, ABRAM KANOF AND BRUNO W. VOLK
WITH THE TECHNICAL ASSISTANCE OF GUTA PERLE 3

The authors have had a large experience with Tay-Sachs disease and give an informative description of the clinical course, pathological characteristics and laboratory findings. Of interest is their observation that the serum aldolase becomes elevated as the disease progresses to the development of muscle atrophy, and that the serum glutamic-oxalacetic acid transaminase is consistently increased throughout, apparently an expression of ganglion disintegration. These biochemical abnormalities may have pathogenic as well as diagnostic implications.

## Review

Pulmonary Embolism and Infarction. A Review of the Physiologic Consequences of Pulmonary Arterial Obstruction. Brent M. Parker and John R. Smith 402

It is quite astonishing that a subject of such clinical importance as pulmonary embolism and infarction has been so little considered in the integrated form of this review. If this neglect arises from the apparent simplicity of the physiologic problems involved, such a notion will soon be dispelled by perusal of this study of the experimental and clinical aspects of the subject. The authors begin with a concise précis of the sites of origin of pulmonary emboli in man. They then review the results of experimental embolization of the lungs in animals (distinguishing the effects of large, medium-sized and miliary emboli, and of embolization per se and resultant infarction). The clinical manifestations first of pulmonary embolism, then of pulmonary infarction are discussed, again with these distinctions clearly made. A final chapter briefly comments on management, stressing the importance of prevention. The review is well documented throughout.

# Seminar on Liver Disease

Study of the impact of diseases of the liver on the metabolic processes within the liver, and consequently on the body as a whole, is still in its early stages but already has proved most rewarding.

Contents continued on page 7

# TAOD FOR MEPROBAMATE"

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This is evident from Dr. Bondy's contribution, which deals particularly with the effects of reduction in liver mass and capacity, notably in advanced cirrhosis, on the metabolism of glucose, amino acids and lipids. The discussion, wherever possible, is in terms of basic metabolic pathways and enzyme activities, and how disturbances in these are expressed clinically and in the usual blood analyses and results of "liver function" tests. The paper gives an enlarged perspective of the complexity of liver functions and of the effects of their derangement.

# Clinico-pathologic Conference

# Case Reports

therapy.

Generalized Scleroderma Associated with Chronic Ulcerative Colitis

RICHARD O. BICKS, MOSHE B. GOLDGRABER AND JOSEPH B. KIRSNER 447

An interesting and thought-provoking case which illustrates several inadequacies of current concepts of the so-called collagen diseases. In this instance typical manifestations of chronic ulcerative colitis preceded onset of symptoms and signs variously indicative of several more or less distinct members of the "collagen disease" group, eventuating in a picture most conveniently classified as generalized scleroderma. The case suggests either that scleroderma and non-specific ulcerative colitis may occur concurrently or that scleroderma occasionally may simulate ulcerative colitis. Available evidence does not convincingly support the view that non-specific ulcerative colitis should be included in the category of "collagen diseases," as currently defined.

- Macroglobulinemia of Waldenström . . . . . . . . . . . . . . . . AVINOAM ZLOTNICK 461

  An interesting case.
- Organic Phosphate Insecticide Poisoning. Residual Effects in Two Cases
  CHARLES S. PETTY 467

Dr. Petty makes his point convincingly, that multiple exposure to certain organic phosphate insecticides, with marked anticholinesterase properties, may lead to permanent and disabling nerve damage. The practical and diagnostic implications need no emphasis.

Contents continued on page 9

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Finnerty, F. A. Jr.: New York State J. Med. 57: 2957 (Sept. 15) 1957.

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Corrin, K. M.: Am. Pract. & Dig. Treatment 8: 721 (May) 1957.

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# CONTENTS continued-March 1958

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NUMBER THREE

Chronic Pulmonary Insufficiency Secondary to Silo-Filler's Disease Gilbert M. P. Leib, W. N. Davis, Trave Brown and Mark McQuiggan	471
An interesting example of the unusual disease which results from exposure to the nitrogen dioxide present in silage gas. Pulmonary function studies and clinical evaluation three years after exposure revealed irreversible pulmonary insufficiency.	
Sjögren's Syndrome. Review of the Literature and Report of a Case with Achalasia of the Esophagus	475
While much has been written about Sjögren's syndrome (rheumatoid arthritis, keratoconjunctivitis sicca, parotitis), this account will be found instructive.	
Effects of Hypophysectomy and of Amphenone Administration in a Child with Func- tioning Metastatic Adrenal Carcinoma	
Edna H. Sobel, Albert E. Renold, John E. Bethune, Joseph J. Hoet,	482
A detailed amount of a matient with functioning material advance engineers treated among other	

A detailed report of a patient with functioning metastatic adrenal carcinoma treated, among other ways, with amphenone. Such clinical response as was obtained was transitory but gave opportunity for further study of the suppressive effect of this agent on adrenal cortical function.

Advertising Index on Page 117



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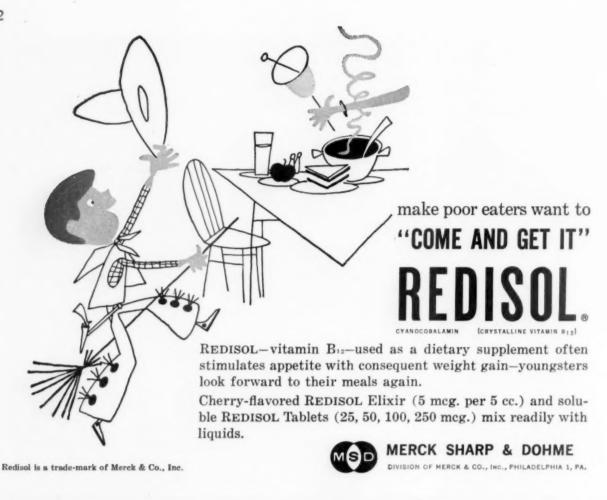
case summary\* A 39-year-old married woman with a history of slight dysmenorrhea and staining intermittently superimposed on a regular 28-day cycle was placed on a regimen of stilbestrol. Staining recurred in spite of increasing dosage. Nearly two months after institution of this therapy a pregnancy of 16-weeks duration was discovered. Spotting continued during the following two weeks. Stilbestrol was then discontinued and treatment with NORLUTIN begun. Staining ceased 3 days after beginning treatment with NORLUTIN. The pregnancy continued uneventfully to full term when she gave birth to a healthy male infant weighing 6 pounds, 5 ounces.

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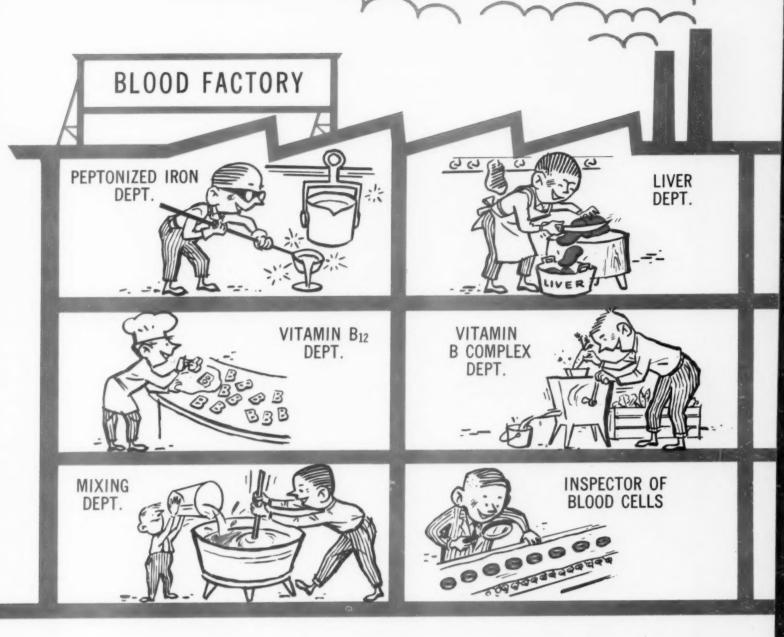
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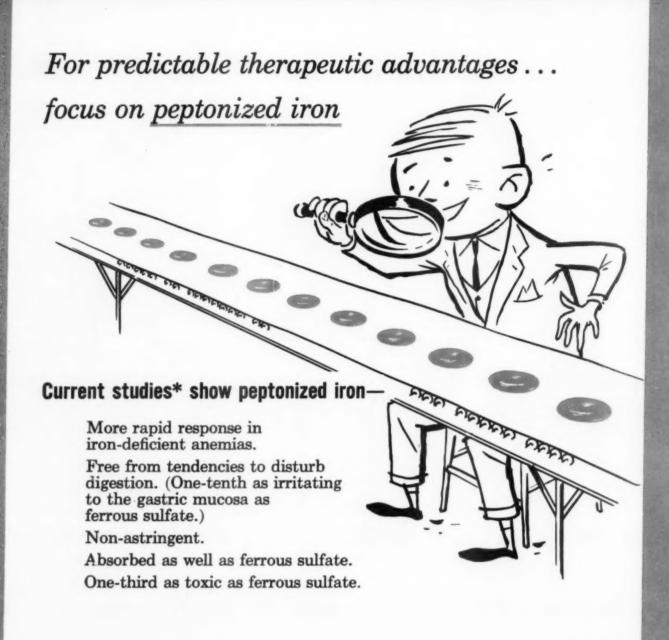
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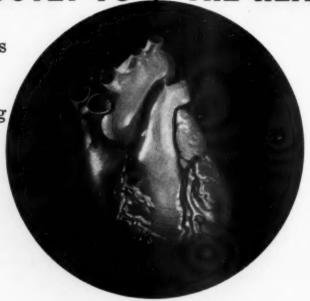


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# a new skeletal muscle relaxant for long-lasting relief with practical dosage

# PARAFLEX

PARAFLEX Chlorzoxazone is 5-chlorobenzoxazolinone, a completely new skeletal muscle relaxant. Acting on the spinal cord, Paraflex selectively depresses the multisynaptic reflex arcs which maintain painful muscle spasm. In the treatment of arthritic, rheumatic or traumatic disorders in which spasm is present, Paraflex provides the physician with an unmatched combination of specific, practical and clinically important advantages.

effective action Clinicians report: Paraflex was found to be a most effective muscle relaxing drug.<sup>1</sup> Improvement was noted in advanced osteoarthritis involving the spine as measured by decrease in muscle spasm and lessening of pain.<sup>2</sup> Symptoms were at least partially alleviated in all patients treated.<sup>3</sup> Therapy with Paraflex provided gratifying relief—no side effects were noted.<sup>4</sup>

long-lasting relief An investigator reports on 148 cases: In most patients, the beneficial effects of Paraflex persisted for approximately six hours.<sup>1</sup>

practical dosage Dosage of Paraflex is usually only one or two tablets, three or four times a day. In experimental studies, Paraflex was from one and one-half to three times as potent as other commonly used muscle relaxants.

side effects rare In a comprehensive study, not one of 148 patients treated with Paraflex had to discontinue therapy because of side effects. To date no side reactions have been encountered. Side effects are uncommon and seldom severe enough to require discontinuation of the drug.

### Clinical results with PARAFLEX

Investigator	Disorder	Number of Patients Treated	Number of Patients Benefited	Comment
Wiesel <sup>2</sup>	advanced osteoarthritis	12	10	less muscle spasm and pain
Holley <sup>3</sup>	wry neck, cervical spondylitis, and disc syndrome	10	10	improvement, ranging from some amelioration of symptoms to profound relief
Settel*	acute low back pain, acute traumatic myofascitis, or osteoarthritis	15	14	response excellent in nine, good in five
Passarelli <sup>6</sup>	degenerative and rheumatoid arthritis	9	9	improvement, with less stiffness and freer motion
Passarelli*	varied arthritic, rheumatic, and traumatic disorders	6	6	less stiffness, less pain
Totals:		52	49	

dosage Paraflex is administered orally in the form of 250 mg. scored tablets. Relief may frequently be obtained on a dosage of one tablet (250 mg.) three or four times a day. Initial dosage for severe muscle spasm should be two tablets (500 mg.) three or four times a day. If adequate response is not obtained with this dose, it may be increased to three tablets (750 mg.) three or four times a day. As improvement occurs, dosage can usually be reduced.

Brochure available on request.

supplied Tablets, scored, orange, bottles of 50. Each tablet contains Paraflex, 250 mg.

reserences 1) Smith, R. T., to be published. 2) Wiesel, L. L., Personal communication. 3) Holley, H. L., Personal communication. 4) Settel, E., Personal communication. 5) Peak, W. P., and Smith, R. T., to be published. 6) Passarelli, E. W., Personal communication.

\*Trade-mark

†U.S. Patent Pending



# Announcing a <u>new</u> anorexigenic specific <u>not</u> a CNS stimulant

"5 times safer (LD/50) than d-amphetamine"



(brand of 1-phenyl-2-aminopropane alginate,† Nordmark)

LEVONOR (1-phenyl, 2-aminopropane alginate, Nordmark) is a new anti-hunger compound that offers a sounder, more effective and more comfortable approach to weight reduction. It has proved remarkably successful in securing cooperation of patients on restricted diets.

# LEVONOR...the appetite suppressant that can be given as late as 8 p.m.



## does not interfere with sleep

In a study of its effects on 173 overweight patients, "none of the patients complained of loss of sleep. In fact when 5 mg. of LEVONOR was given at 8 p.m. no interference with sleep was noted; night hunger was markedly diminished." This is a unique advantage since it is in the evening when most obese patients are tempted to break their diet.

### no CNS overstimulation

LEVONOR has no effect on the mood of the patient. It does not overstimulate the cerebral cortex, thus avoiding jitteriness, tenseness, nervousness and disturbance of sleep.

### depression of appetite is its primary effect

Unlike d-amphetamine, LEVONOR is not a central nervous system stimulantits primary effect is to depress the appetite. Impressive results, even with late evening doses, are obtained without the addition of sedatives.1-5

## five times safer than dextro-amphetamine

LEVONOR's much greater safety (LD/50) and, concomitantly, its far greater freedom from side effects have been striking findings in extensive toxicity studies.1

## here are typical clinical results with LEVONOR:

### STUDY NO. 11

Number of p	at	ier	its	0					173
Average daily	y	dos	se	0	a	2-	31	tak	lets
					(!	5 n	ng	. ea	ach)
Average dura									
treatment	0	0					6	W	eeks
Average weel	kly	y W	vei	gh	t				
loss						.2	-2	1/2	lbs.
Side effects									9*
*Minin	112	ha l	387	dos	90	0 0	die	efi	ment

### STUDY NO. II2

Number of p	at	ier	nts						52
Average dail	ly (	dos	se		1				lets
Average dur	ati	on	of		10	, 11	ug.	· Ce	icii,
treatment							9	we	eks
Average wee	kly	v v	vei	gh	t				
loss							2	2.1	lbs
Side effects									1
		*	Ad	jus	tec	w	ith	dos	sage

economy and low dosage of LEVONOR make it possible to administer this drug long enough to favorably alter the patient's eating habits.

### Administration and Dosage:

Average dose: 5 to 10 mg. twice daily.

### Bibliography

- Sc. Exhibit, N. Y. State Med. Meeting, Feb. 18-21, 1957.
   Pomeranze, J.: Report 807: 1957.
   Frohman, I. P.: Report 315: 1957.

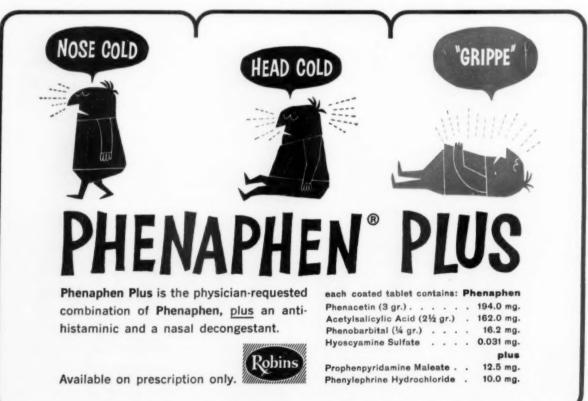
- Dwyer, Thomas: Report 912: 1957. Gadek, R. J.: Report 186: 1957.
- Sc. Exhibit, Mich. State Med. Soc. Meeting Sept. 25-27, 1957.

†Patent Pending



NORDMARK Pharmaceutical Laboratories, Inc., Irvington, N. J.





# Monilial overgrow is a factor

# Achrostatin\*V

Combines ACHROMYCIN V with NYSTATIN

CAPSULES contain 250 mg. tetracycline HCl equivalent (phosphate-buffered) and 250,000 units Nystatin. OBAL SUSPENSION (cherry-mint flavored) Each 5 cc. teaspoonful contains 125 mg. tetracycline HCl equivalent (phosphate-buffered) and 125,000 units Nystatin.

### DOSAGE:

Basic oral dosage (6-7 mg, per lb, body weight per day) in the average adult is 4 capsules or 8 tsp. of Achrostatin V per day, equivalent to 1 Gm, of Achromycin V.





# **HELPS** PALSIED **PATIENTS** "LIVE AGAIN"

rated the best single drug for the palsied patient 1

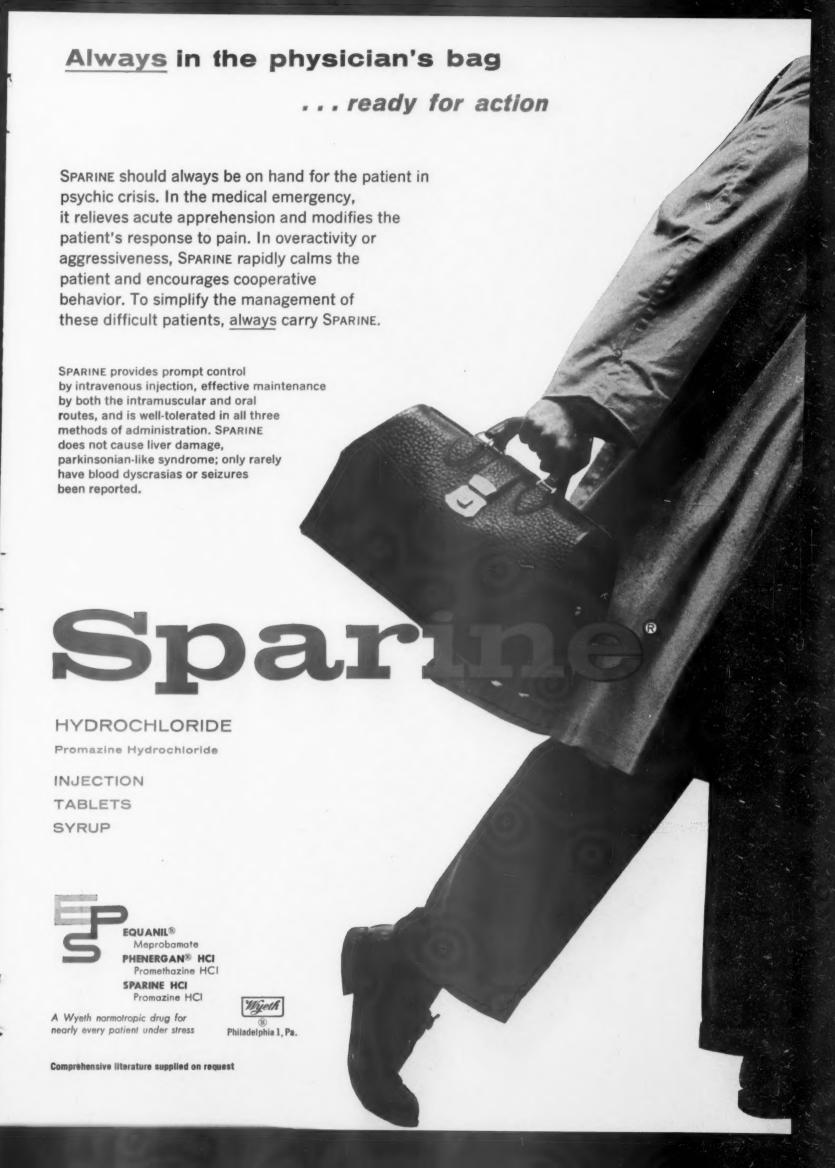
- · Well tolerated and highly effective, COGENTIN "should be added to the treatment program of every patient with paralysis agitans." 2
- COGENTIN gives maximal symptomatic relief in all types of parkinsonism-whether postencephalitic, idiopathic, or arteriosclerotic.
- COGENTIN provides highly selective action such as no other current drug affords.2 It is often of benefit in rigidity, muscle spasm, even in severe tremor.3 The contracture of parkinsonism is relieved and posture is improved.3
- · With the help of COGENTIN, therapy with tranquilizers can often be continued in patients in whom trembling would otherwise force reduction or withdrawal.4

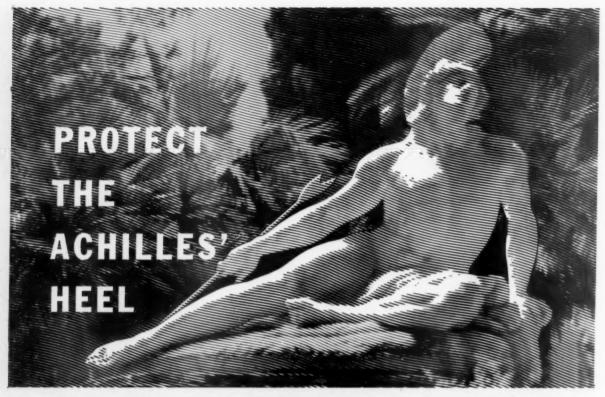
As COGENTIN is long-acting, one dose daily may be sufficient.

Supplied: as 2 mg. quarter-scored tablets in bottles of 100 and 1000.

M. Clin. North America 38:485 (March) 1954.
 J.A.M.A. 162:1031, 1956.
 J.A.M.A. 156:680, 1954.
 Yale J. Biol. & Med. 28:308, 1955/56.







# OF EVERY AGING PATIENT

The combination of declining gonadal function and increased vulnerability to malnutrition conspire to accelerate the aging process. You can protect the aging patient by prescribing a "Clusivol" Geriatric capsule daily.

There are four important features of "Clusivol" Geriatric:

- 1. Vitamins 12 important nutritional supplements, notably vitamins A and D, the factors of the B complex, and vitamin C.
- 2. Minerals and trace elements -10 protective factors to ensure optimal blood and bone building.
- 3. Amino acids lysine and methionine, key amino acids usually lacking in finicky geriatric diets.
- **4. Gonadal steroids** estrogen and androgen in small quantities to restore the integrity of the body mechanism.

Supplied: No. 294 - Capsules, bottles of 100 and 1,000.

# "CLUSIVOL" GERIATRIC

potent nutritional elements with steroids

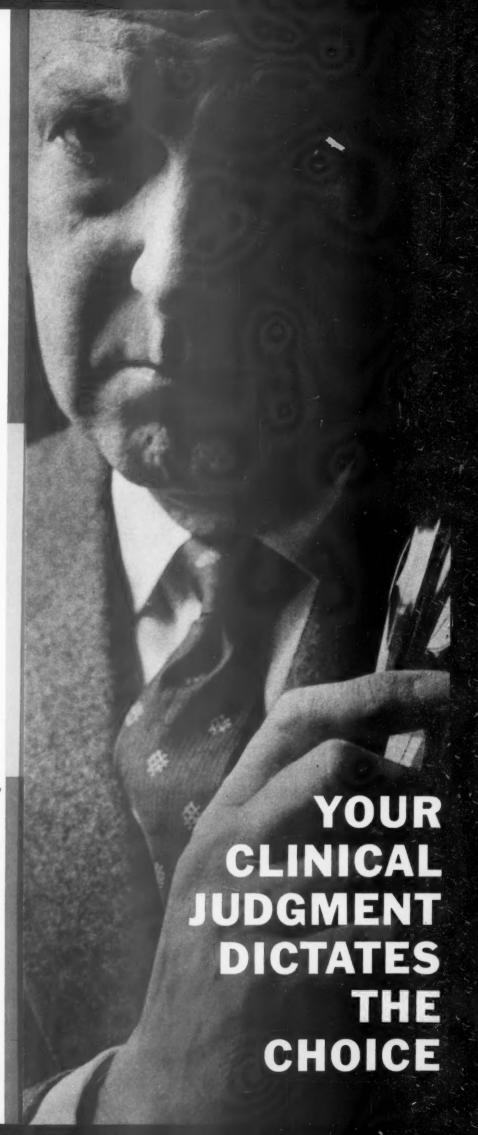


AYERST LABORATORIES • NEW YORK 16, N. Y. • MONTREAL, CANADA

in common mixed infections ...tetracycline phosphate alone

in potentially
serious
infections
...tetracycline
phosphate
plus
novobiocin

for the
7 moniliasusceptible
types
...tetracycline
phosphate
plus
nystatin



in common mixed infections ...tetracycline phosphate alone

PANMYCII Phosphate

for children

PANMYCII Syrup

in potentially serious infections

...tetracycline phosphate plus novobiocin PANALBA\*

for children:

PANALBA Granules

for the 7 moniliasusceptible types

...tetracycline phosphate plus nystatin COMYCIN'

Upjohn

The Upjohn Company, Kalamazoo, Michigan

THADEBARK ACC. O. T. BAT. OF

IN\*

BROAD-SPECTRUM TETRACYCLINE IN ITS MOST EFFICIENT FORM

Produces more tetracycline in the blood with no more in the dose. No calcium to depress blood levels. Basic broad-spectrum therapy in bronchitis, pharyngitis, otitis media, tonsillitis, and other common respiratory infections.

1. Welch, H.; Wright, W. W.; and Staffa, A. W.: Antiblotic Med. & Clin. Therapy 4:620, 1957.

# A\* A KM

THE BREADTH OF PANMYCIN PHOSPHATE PLUS THE ANTIMICROCOCCAL DEPTH OF ALBAMYCIN<sup>†</sup>

Offers maximum antimicrobial action at the earliest possible moment. The antibiotic preparation of first resort in pneumonia of unknown etiology, carbuncles, multiple furunculosis, cellulitis, and infections resistant to previous therapy.

TRADEMARK, REG. U. S. PAT. OFF. - THE UPJOHN BRAND OF CRYSTALLINE NOVOBIOCIN SODIUM

PANMYCIN PHOSPHATE PLUS THE ANTIMONILIAL PROTECTION OF NYSTATIN

The logical choice for patients requiring high doses of antibiotics or prolonged antibiotic therapy; for patients with previous monilial complications; for diabetics; patients on corticoids; the pregnant, debilitated, or elderly; and for infants, especially the premature.

# THE CHOICE OF A SYSTEMIC ANTIBIOTIC IS A MATTER OF CLINICAL JUDGMENT

# 1. PANMYCIN PHOSPHATE IN COMMON MIXED INFECTIONS

**USUAL DOSAGE:** ADULTS: 250 mg. every 6 hours or 500 mg. every 12 hours. CHILDREN: Approximately 8 mg. per pound of body weight daily, in four equally divided doses every 6 hours, or two equally divided doses every 12 hours.

SUPPLIED: CAPSULES: 250 mg. in bottles of 16 and 100; 125 mg. in bottles of 25 and 100.

**PANMYCIN KM SYRUP:** Each teaspoonful (5 cc.) contains tetracycline equivalent to 125 mg. tetracycline hydrochloride, and potassium metaphosphate, 100 mg., mint flavor, in 2 fluidounce and pint bottles.

# 2. SERIOUS INFECTIONS

**USUAL DOSAGE:** ADULTS: 1 or 2 capsules three or four times a day, depending on the type and severity of the infection. CHILDREN: Proportionately less.

**SUPPLIED:** Each powder-blue-and-brown capsule contains Panmycin (tetracycline) Phosphate complex equivalent to 250 mg. tetracycline hydrochloride, and Albamycin (as novobiocin sodium) 125 mg.; in bottles of 16 and 100.

Also available: **PANALBA KM GRANULES** (Pediatric). When reconstituted, each 5 cc. teaspoonful contains Panmycin equivalent to tetracycline hydrochloride, 125 mg. and Albamycin (as novobiocin calcium) 62.5 mg., and potassium metaphosphate 100 mg.; in pleasantly flavored vehicle. Dosage is based upon amount of tetracycline—6 to 8 mg. per pound of body weight per day in 2 to 4 equally divided doses.

# 3. COMYCIN FOR THE 7 MONILIA-SUSCEPTIBLE TYPES

USUAL DOSAGE: ADULTS: 1 or 2 capsules every 6 hours. CHILDREN: Proportionately less.

**SUPPLIED:** Each brown-and-pink capsule contains tetracycline phosphate complex, equivalent to 250 mg. tetracycline hydrochloride; nystatin 250,000 units. In bottles of 16 and 100.





# HYPERTENSIVE...yet controlled with safer combination therapy

"objective relief...gratifying"

Rauvera—the combination of alseroxylon and alkavervir—is much more effective than either drug alone. This combination produces "no postural hypotension, no organ toxicity, and no sensitization reactions. Tolerance does not develop on prolonged administration... hypotensive action is steady and prolonged and persists over the entire twenty-four hours." Rauvera therapy can be continued over long periods of time.

"subjective relief...even more so"

Alseroxylon and alkavervir "when combined produce mutual reinforcement so that...more severe cases respond," yet "side effects are minimal." Most patients feel better, are less tired and are free from headaches. Anxiety and tension are relieved...pulse rate slowed...such symptoms as "heart consciousness," tinnitus, vertigo, giddiness and insomnia disappear rapidly—leaving a calm and relaxed patient.

### RAUVERA

1 mg. alseroxylon-3 mg. alkavervir in each scored tablet.

1. Bendig, A.: New York State J. M. 66:2523, 1956. 2. La Barbera, J. F.: Med. Rec. and Ann. 50:242, 1956. 3. Gilchrist, A. R.: Brit. M. J. No. II:1011, 1956.



"an ideal compound

for use in common

urinary tract infections."\*



Azo Gantrisin provided "prompt and effective clearing of organisms and pyuria"\* plus "dramatic relief of bladder and urethral symptoms"\* in 221 (97%) of 228 patients with urinary tract infections.

Azo Gantrisin is particularly useful in the treatment of cystitis, urethritis and prostatitis. It is equally valuable following urologic surgery, cystoscopy and catheterization because it provides effective antibacterial action plus prompt pain relief.

AZO GANTRISIN®-500 mg Gantrisin (brand of sulfisoxazole) plus 50 mg phenylazo-diamino-pyridine HCl

\*F. K. Garvey and J. M. Lancaster, North Carolina M. J., 18:78, 1957.

# AZO GANTRISIN 'Roche'

ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC • NUTLEY • N. J.
ORIGINAL RESEARCH IN MEDICINE AND CHEMISTRY

overwhelmingly specified by generalists and specialists

# METICORTEN°

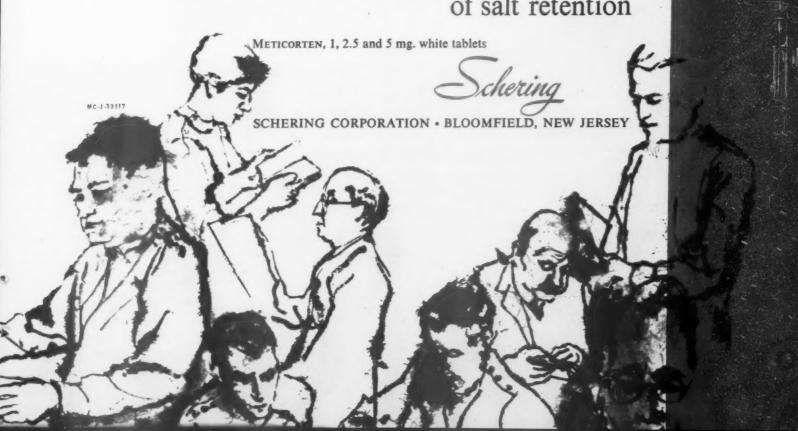
prednisone

# a standard steroid overwhelmingly acclaimed

by

- ... Internists in rheumatoid arthritis, rheumatic fever and systemic lupus erythematosus
- ... Allergists in urticaria, angioedema, drug reactions and allergic rhinitis
- ... Ophthalmologists in uveitis, choroiditis and chorioretinitis
- ... Dermatologists in pemphigus, erythema multiforme, atopic eczemas and contact dermatoses
- ... Chest Physicians in bronchial asthma, pulmonary fibrosis and emphysema

and by general practitioners for virtual absence of salt retention



# NEW "Single-R"

for use



- Symptomatic relief of aches, pains, fever, coryza, and rhinorrhea associated with upper respiratory tract infections.
- Prevention of secondary pyogenic infections due to tetracycline-sensitive organisms which often follow viral infections of the upper respiratory tract.

Bristol Laboratories inc. syracuse, new york

# MEDICATION

in "flu," "grippe," "virus" and the common cold

# Tetrex-APC

TETRACYCLINE PHOSPHATE COMPLEX WITH PHENYLTOLOXAMINE AND APC

### Each TETREX-APC WITH BRISTAMIN Capsule contains:

### A broad-spectrum antibiotic

### An established analgesic-antipyretic combination

### A dependable antihistamine

Dosage: Adults: 2 capsules at onset of symptoms, followed by 2 capsules 3 or 4 times a day for 3 to 5 days. Children, 6 to 12 yrs.: One-half adult dose.

Supplied: Bottles of 24 and 100 capsules.

# GOING

















# with STERA

brand of prednisolone

ARTHRITIC patients on STERANE can regain an ability to "go places and do things"—unsurpassed by previous corticoids—with minimal incidence of mineralocorticoid complications.

White, scored 5 mg. tablets (bottles of 20 and 100); pink, scored 1 mg. tablets (bottles of 100).



Pfizer PFIZER LABORATORIES, Brooklyn 6, New York Division, Chas. Pfizer & Co., Inc.

# CIBA antihypertensive agents reduce cholesterol and lipoprotein levels

Reports of the cholesterol- and lipoprotein-reducing properties of Serpasil, Apresoline and the ganglionic blockers have come from several groups of investigators. Corcoran et al.1 noted that atherosclerotic complications were less common in those with good responses to antihypertensive treatment than those with fair or poor response. Under Apresoline therapy, the average depression of cholesterol in 112 unselected hypertensive patients was 29 mg.; "... among the 66 with high control levels the fall was 48.2 mg. in the first six months, and thereafter 43.5 mg. per 100 ml. of plasma."2 Within a group of 9 geriatric patients given reserpine, "... seven patients showed a definite drop in the blood level of the heavier and more compact lipoprotein molecules . . . "3

When planning a program to reduce blood-pressure levels, consider the added benefits of these CIBA antihypertensive agents:

# Serpasil'... Apresoline

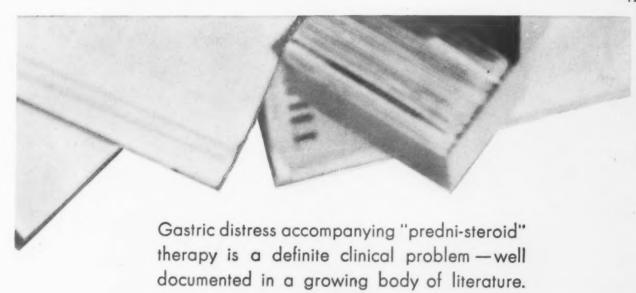
 Corcoran, A. C., Lewis, L. A., Dustan, H. P., and Page, I. H.: Ann. New York Acad. Sc. 64:620 (Nov. 16) 1956.
 Perry, H. M., Jr., and Schroeder, H. A.: J. Chronic Dis. 2:520 (Nov.) 1955.
 Galioni, E. F.: California Med. 85:97 (Aug.) 1956.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
SERPASIL® (reserpine CIBA)

evidence<sup>3</sup>
indicates

# BUFFERED

Predni-steroids for rheumatoid arthritis.....



\*"In view of the beneficial responses observed when antacids and bland diets were used concomitantly with prednisone and prednisolone, we feel that these measures should be employed prophylactically to offset any gastrointestinal side effects."—Dordick, J. R. et al.: N. Y. State J. Med. 57:2049 (June 15) 1957. \*"It is our growing conviction that all patients receiving oral steroids should take each dose after food or with adequate buffering with aluminum or magnesium hydroxide preparations."—Sigler, J. W. and Ensign, D. C.: J. Kentucky State M. A. 54:771 (Sept.) 1956.

\*"The apparent high incidence of this serious [gastrie] side effect in patients receiving prednisone or prednisolone suggests the advisability of routine co-administration of an aluminum hydroxide gel."—Bollet, A. J. and Bunim, J. J.: J. A. M. A. 158:459 (June 11) 1955.

One way to make sure that patients receive full benefits of "predni-steroid" therapy plus positive protection against gastric distress is by prescribing CO-DELTRA or CO-HYDELTRA.

# ·· Co-Deltra

multiple compressed tablets

provide all the benefits of "Predni-steroid" therapy plus positive antacid protection against gastric distress

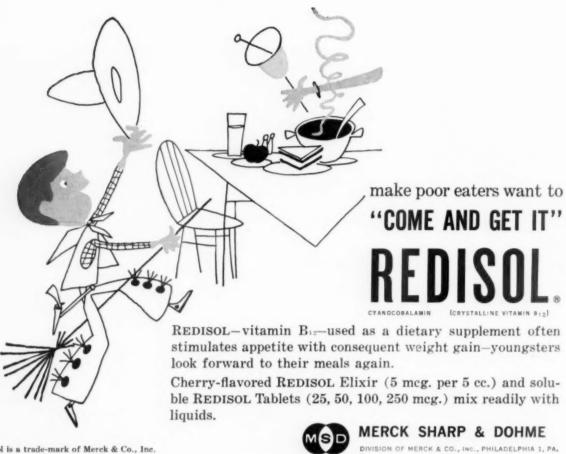
# Co-Hydeltra PREDNISOLONE BUFFERED



2.5 mg. or 5.0 mg. of prednisone or prednisolone, plus 300 mg. of dried aluminum hydroxide gel and 50 mg. magnesium trisilicate, in bottles of 30, 100, 500.

MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa.





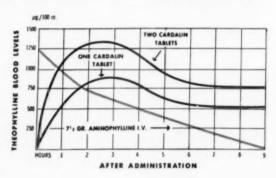
Redisol is a trade-mark of Merck & Co., Inc.

## Orally... higher and more sustained aminophylline blood levels than those produced intravenously

Cardalin utilizes two synergistic protective factors to permit administration of high oral doses of aminophylline without the usual side effects of nausea, gastric irritation and vomiting.

## CARDALIN

... proven effective clinically whenever high blood concentrations of aminophylline are desired . . . as in congestive heart failure, cardiac edema, paroxysmal dypsnea, angina pectoris, myocardial infarction, heart block and bronchial asthma.



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

Each Cardalin tablet supplies: Aminophylline, 5.0 gr.; Aluminum hydroxide, 2.5 gr.; Ethyl aminobenzoate, 0.5 gr.

Also available, Cardalin-Phen.



Irwin, Neisler & Co.

Decatur, Illinois

in anti-inflammatory effects with lower dosage (averages 1/3 less than prednisone)

The Achievements of

# AMISTOCOM

Triamcinolone LEDERLE

in the collateral
hormonal effects associated
with all previous corticosteroids

- No sodium or water retention
- No potassium loss
- No interference with psychic equilibrium
- Low incidence of peptic ulcer and osteoporosis

Aristocort is available in 2 mg. scored tablets (pink), bottles of 30; and 4 mg. scored tablets (white), bottles of 30 and 100.



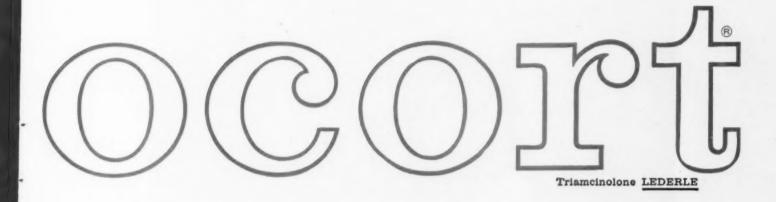
The Achievement in Skin Diseases: In a study of 26 patients with severe dermatoses, ARISTOCORT was proved to have potent anti-inflammatory and antipruritic properties, even at a dosage only 3/3 that of prednisone.1... Striking affinity for skin and tremendous potency in controlling skin disease, including 50 cases of psoriasis, of which over 60% were reported as markedly improved2...absence of serious side effects specifically noted.1,2,3

The Achievement in Rheumatoid Arthritis: Impressive therapeutic effect in most cases of a group of 89 patients4...6 mg. of ARISTOCORT corresponded in effect to 10 mg. of prednisone daily (in addition, gastric ulcer which developed during prednisone therapy in 2 cases disappeared during ARISTOCORT therapy).5

- 1. Rein, C. R., Fleischmajer, R., and Rosenthal, A. L.: J. A. M. A.
- 165:1821, (Dec. 7) 1957.
   Shelley, W. B., and Pillsbury, D. M.: Personal Communication.
   Sherwood, A., and Cooke, R. A.: Personal Communication.
   Freyberg, R. H., Berntsen, C. A., and Hellman, L.: Paper
- presented at International Congress on Rheumatic Diseases, Toronto, June 25, 1957.
- 5. Hartung, E. F.: Personal Communication.6. Schwartz, E.: Personal Communication.
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- 8. Hellman, L., Zumoff, B., Kretshmer, N., and Kramer, B.: Paper resented at Nephrosis Conference, Bethesda, Md., Oct. 26, 1957.
- 9. Îbid.: Personal Communication.
- 10. Barach, A. L.: Personal Communication.
- 11. Segal, M. S.: Personal Communication.
- 12. Cooke, R. A.: Personal Communication.
- 13. Dubois, E. L.: Personal Communication.

The Achievement in Respiratory Allergies: "Good to excellent" results in 29 of 30 patients with chronic intractable bronchial asthma at an average daily dosage of only 7 mg.6... Average dosage of 6 mg. daily to control asthma and 2 to 6 mg. to control allergic rhinitis in a group of 42 patients, with an actual reduction of blood pressure in 12 of these.<sup>7</sup>

The Achievement in Other Conditions: Two failures, 4 partial remissions and 8 cases with complete disappearance of abnormal chemical findings lead to characterization of ARISTOCORT as possibly the most desirable steroid to date in treatment of the nephrotic syndrome.<sup>8,9</sup>... Prompt decrease in the cyanosis and dyspnea of pulmonary emphysema and fibrosis, with marked improvement in patients refractory to prednisone.<sup>10,11,12</sup>... Favorable response reported for 25 of 28 cases of disseminated lupus erythematosus.<sup>13</sup>



Depending on the acuteness and severity of the disease under therapy, the initial dosage of ARISTOCORT is usually from 8 to 20 mg. daily. When acute manifestations have subsided, maintenance dosage is arrived at gradually, usually by reducing the total daily dosage 2 mg. every 3 days until the smallest dosage has been reached which will suppress symptoms.

Comparative studies of patients changed to ARISTOCORT from prednisone indicate a dosage of ARISTOCORT lower by about ½ in rheumatoid arthritis, by ½ in allergic rhinitis and bronchial asthma, and by ½ to ½ in inflammatory and allergic skin diseases. With ARISTOCORT, no precautions are necessary in regard to dietary restriction of sodium or supplementation with potassium.

ARISTOCORT is available in 2 mg. scored tablets (pink), bottles of 30; and 4 mg. scored tablets (white), bottles of 30 and 100.



"Since we've had him on NEOHYDRIN he can walk without dyspnea. I wouldn't have believed it possible a month ago."

oral organomercurial diuretic

NEOHYDRIN®
BRAND OF CHLORMERODRIN



# ACHROCIDIN

TETRACYCLINE-ANTIHISTAMINE-ANALGESIC COMPOUND LEDERLE

A versatile, well-balanced formula offering in one tablet the drugs often prescribed separately for treating upper respiratory infections.

Traditional and nonspecific nasopharyngeal symptoms of malaise and chilly sensations are rapidly relieved, and headache, muscular pain, and pharyngeal and nasal discharges are reduced or eliminated.

Early effective therapy is provided against such bacterial complications as sinusitis, otitis, bronchitis and pneumonitis to which the patient may be highly vulnerable at this time.

Adult dosage for ACHROCIDIN Tablets and new, caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children reduced according to weight and age.

Available on prescription only.

**TABLETS** (Sugar-coated) Each tablet contains:

ACHROMYCIN®	
Tetracycline	125 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Salicylamide	150 mg.
Chlorothen Citrate	25 mg.
Bottles of 24 and 100	

**SYRUP** (Lemon-lime flavored)
Each teaspoonful (5 cc.) contains:
ACHROMYCIN® Tetracycline

equivalent to	
tetracycline HCl	125 mg
Phenacetin	
Salicylamide	150 mg.
Ascorbic Acid (C)	25 mg.
Pyrilamine Maleate	
Methylparaben	4 mg.
Propylparaben	1 mg.
Bottle of 4 oz.	



## INTENSIFIED BROAD-SPECTRUM ANTIBIOTIC CONTROL

# Tetreycling Phosphate Complex U. S. Pat. 2,781,809

often the difference between rapid and delayed response

blood levels practically double those of tetracycline hydrochloride within 1-3 hours / maintains higher blood levels than tetracycline hydrochloride up to 24 hours /a single, highly efficient antibiotic permitting simple, flexible dosage /equally effective on convenient b.i.d. schedule, as on a q.i.d. schedule /practically sodium-free—pure compound—not a mixture.

Supplied:TETREX Capsules containing the equivalent of 250

Supplied:TETREX Capsules containing the equivalent of 250 mg. tetracycline HCI activity; bottles of 16 and 100. New TETREX Pediatric Capsules containing the equivalent of 100 mg. tetracycline HCI activity; bottles of 25 and 100.

To the point
of infection
as in acute
respiratory diseases



# Tetracycline Phosphate Complex 250-100 mg. CAPSULES





# Tetrex-APC WITH BRISTAMIN®



## INTENSIFIED TETRACYCLINE CONTROL

Integrated with analgesia control / antihistamine control

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\*T. R. Robie, paper read at First Marsilid Symposium, New York City, November 29, 1957

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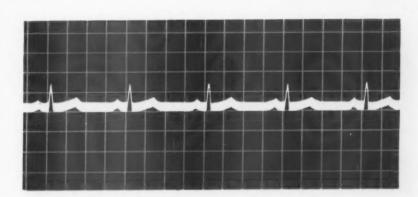
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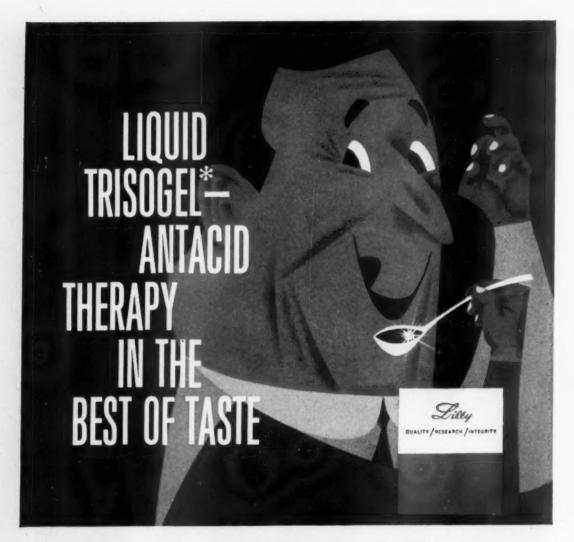
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## Editorial

# The Specificity Hypotheses of Psychosomatic Medicine

Koch's Postulates Revisited

The ills popularly classed as psychosomatic have at least one common factor, they are uncommonly hard to treat. While some have yielded in part to therapy based on endocrinology, microbiology, biologic metabolic antagonists or the knife; others have yielded so slightly that the best these conventional modalities of therapy can offer, whether in the setting of a teaching center or of rural practice, is palliation.\*

Intractability provides no small reason for the general interest that has greeted volumes giving pioneering explorations by psychodynamically oriented physicians of these ills which were previously in the province of the internist, the surgeon and the pediatrician [1–3]. While the interpretive critique in many of these explorations is perhaps not that demanded by older modalities of clinical investigation, the historically minded physician has often tempered his doubts with the recognition that critique only comes with time and that dynamically oriented psychiatry is young.

In the 1920's and 1930's, few teaching hospitals could boast a psychiatrist whose principal clinical and investigative responsibility lay on the medical service. Psychoanalytic training in these few was an exception.

The post World War II psychodynamic enthusiasm brought foundation support for full time assignment of analytically oriented psychiatrists to a handful of university hospital medical services. A bare ten years later, the teaching medical service without a psychodynamic team sometimes feels as deprived as it might have without a bacteriologic team half a century ago.

From medicine and pediatrics, spread to surgical services, both general and special, is progressing. Today it is not unheard of to find a surgeon almost as familiar with the concepts of Freud and Sullivan as he is with those of Pasteur and Lister. The resultant change in the atmosphere of general hospital training [4] may be keenly felt by a retrospective comparison of the prevalent ward rounds vocabulary of many a senior resident with that of the attending man.

A comparable change has occurred in the atmosphere of research. The addition of the continuously expanding support of the National Institute of Mental Health to that of other private and public agencies has provided opportunities for psychosomatic clinical investigation of scope and elaborateness not previously available. Animal studies, projective psychological studies, pharmacodynamic studies, neurosurgical and neurophysiologic studies, interview studies ranging from a single hour to five year psychoanalyses interlock in endless per-

<sup>\*</sup> Indeed, in the design of some ongoing psychosomatic research, one wonders whether intractability is as good an admission ticket as a promising psychodynamic lead, vide the increasing study of neoplastic disease.

mutations in psychosomatic journals and in applications for research grants.

In the midst of this plenty, the physician who travels may find small signs which, although expressible in the language of ward rounds, perhaps would be plainer in the language of Wall Street.

Thus, in some medical centers most liberally supplied with facilities for psychosomatic investigation, if one asks a service chief about the role of psychodynamics in the long range handling of a given condition, he may answer, "Which patients do you mean? Our research patients? Our dispensary patients? The attending staff's private patients?"

Such questions (particularly when given in answer by a chief sympathetic to dynamic psychiatry), do not reflect the clarity in definition of pathogenetic significances and management values that he might give for the more conventional modalities of therapy.

If in the medical center these issues are not wholly clarified, to the practicing physician they are even more clouded; the descriptive terminology of the psychosomaticists often seems fanciful and the observational bases limited and insecure. It does not help the man in practice to have the historian point out that the psychosomatics probably appear no more fanciful than microbiologic thinking appeared in the days when the controversy over spontaneous generation of microorganisms was acute.

The man in practice might historically counter thus: Like focal infection, body-mind interactions in disease are older in literature than ancient Greece. Both the arch theorist\* and the arch clinical observer [5] of the Greek age write of psychosomatics in a fashion which augurs favorably for subsequent developments in theory and practice. But when that Athenian therapist, in his basket chair, told the patient:

Then sit you down upon that sacred bed-Come now, you tell me something of your habits-

Excogitate upon your affairs-

Let your thoughts range freely through the air-

this approach to the psyche ended up, at the hand of the arch comic poet, in "The Clouds."\*

To return via the nineteenth century to the present, no sensitive clinician doubts that psychic events can bear significant relations both to appearance and intensity of disease manifestations. But today's psychosomaticist goes further in two ways, first by suggestion of relations between specific psychic configurations and specific disease entities; secondly, with today's "sacred bed" go variously formulated technics of intensive psychotherapy whose proponents believe potent to alter psychic configurations sufficiently to warrant the use of the phrase "change of character structure."

Faced with intractability in the diseases and a baffling terminological prolixity in description of psychic configurations and therapeutic maneuvers, both the scientist and the physician today have reason to ask: (1) whether or not psychosomatic explorations have given base for the development of a logic of description adequate to relate the psychic configurations to the disease sequences; (2) whether or not these investigations have yielded a more effective method of attack, either by way of prevention or treatment.

The nineteenth century postulates of Koch provided a serviceable logic by which microbiologic medicine achieved scientific respectability. Medical respectability t was assured by the tools immediately put in the hands of the doctor, asepsis and antisepsis. Without Procrustean distortion of analogies between the special logical demands of psychiatric and microbiologic levels of observations, have we as yet portends of any comparable achievement for psychosomatic medicine?

<sup>\*</sup> That the arch theorist was not unskilled in clinical observation is evidenced by the recommendation for management of hangovers among intellectuals in the beginning of the Symposium [The Works of Plato (edited by EDMAN, I.) pp. 338-339. New York, 1928. Modern Library.]

<sup>\*</sup> Aristophanes, The Clouds. (Translated by Rogers, B. B.) pp. 287, 311, 331, 337. Cambridge, 1950. Harvard University Press.

A productive modern worker in neuroanatomic correlates of behavior [6] as well as the theory and practice of dynamic psychiatry has recently called attention ([7], p. 365) to certain details in Aristophane's treatment of the therapeutic methodology of the "just and unjust

<sup>†</sup> There is little question that the physician has come a long way in approaching Abraham Flexner's scientific ideal in the last half century (vide ATCHLEY, D. W. The healer and the scientist, The Saturday Review, Jan. 9, 1954), but that the healer and the scientist are always going to have a somewhat different outlook can be verified by comparing the type of boy one meets in a medical school dining room with his counterpart in the dining room of the Massachusetts Institute of Technology.

#### CAUSE, PROCESS AND TRANSACTION

In the popular mind, the triumph of microbiology was the finding of causes for diseases.

The last decade has seen the precipitous disappearance of the word "cause" from the writings of workers in psychosomatic medicine. In replacement is emerging a terminology which doubtless would prove much more satisfactory to the late A. N. Whitehead [8] and perhaps to Henri Bergson [9].

Thus, in a recent and already classic study of the psychologic process in ulcerative colitis [10], there is an extensive footnote devoted to the validity of a "transactional" description, in which the organism is observed "in process with environment." The author urges the revision of the familiar pathogenetic descriptions in terms of interaction of multiple factors in favor of descriptions accepting the "organisms and environment as a common system, . . . in terms of open systems, dynamic steady states, feed back mechanisms and multi-factorial concepts . . . "This is about as far from saying "this man's emotional problems caused his colitis" as one can get.

However, in the popular mind, the word 'cause' still remains in daily use, and for the daily thinking of the physician, so does its polysyllabic synonym. In this daily use there is a validity which is not inconsistent with "multiple factor" conceptualization; the cause usually means the factor or factors most accessible to manipulation toward improving an unsatisfactory state of affairs.

Thus, that lobar pneumonia can be described in a "transactional" fashion does not invalidate "pneumococcal etiology." Today, with drugs which reliably eradicate pneumococcus in vivo and to which it does not develop resistance, the monumental explorations of pneumococcal immunochemistry which abound in older volumes of the Journal of Experimental Medicine are rarely cited in our teaching hospitals, except when a hypogammaglobulinemic failure of this aspect of "the pneumonia transaction" requires that something be done. The socio-economic-environmental aspects of the "pneumonia transaction" were perhaps better described in the compressed paragraphs of the first edition of Osler's text [11] than in many of today's works.

Contrast the status of the disease with which Koch's name is linked. Despite recent and rapid progress in chemotherapy, nothing is yet avail-

able against tuberculosis of comparable efficacy to penicillin against the pneumococcus. One of today's leading students of the laboratory behavior of Koch's bacillus [12] has stressed eloquently the importance of such factors as animal protein intake and stress of racial persecution in the understanding of world-wide trends in incidence, and has suggested that war occasioned community anxiety without the privation of battle or conquest may warrant consideration as a significant epidemiologic variable. Here, the statement "Koch's bacillus causes tuberculosis" is insufficient to give either the practicing physician or the public health officer the maximum available efficacy in care or control measures. Both need a more cumbersome "transactional" or "interactional" statement.\*

One cannot help suspecting that the more the existing state of knowledge demands that the physician talk like a philosopher of science, the less available are effective measures of prevention and cure.

When, with an appropriately timed antibiotic, the physician can guide a patient with lobar pneumonia back to work in a week, he is glad to be able to predict for the patient, for all practical purposes, the same state of health (or better) than before. While agreeing that "the linear must be replaced with the spiral—no system is ever again exactly the same as it was before—the patient is never restored to the same state of health—" [10], the physician cannot help rejoice that this

\* Some readers may find linguistic wonder (in view of Latin meanings) at the growing preference to attach the prefix "trans-" instead of "inter-" to "-action" in psychosomatic terminology [10].

An epistemologic as well as heuristic wonder may also be entertained [See Meyerson's classic discussion (Meyerson, E. Identité' et Realité', F. Alcan, Paris, 1926, p. 438 et. seq.) also Cassirer's Substanzbegriff und Funktionbegriff (Berlin, 1910) and Whitehead's Principles of Natural Knowledge (Cambridge, 1925)].

It is far from clear that advances in biology have come from interposing Latin or Greek intermediaries between the concrete expressiveness of everyday language and the unique expressiveness of mathematics and symbolic logic for abstract relations.

I have often thought that the propositional functions of the symbolic logician (cf. Lewis, C. I. and Langford, C. H., Symbolic Logic, Century, New York, 1932, Chapter V et. seq.) would be an elegant way to express degrees of probability which may be attached to evidence in clinical investigation. However, on the ward and in the laboratory, the symbolism is not widely known, it is something of a trick to learn, and we can still work effectively with a less condensed but perhaps more understandable terminology.

philosophically correct statement no longer necessarily must spiral through the empyemic, endocarditic and meningitic phenomena which in the preantibiotic age left so many patients for all practical purposes in a very different state of health.

Thus, in looking to psychosomatic studies for help in management of clinically intractable ills, the physician will certainly not object to any complexity of terminology if it gives him Denkmittel\* to work with. And if, in the popular mind, this means identifying "causes," such identification can be no more objectionable than the identification of the master switches and fuse boxes in a useful electrical system.

#### THE ISOLATION OF THE ORGANISM

#### From Personality Profile to Nuclear Conflict

Such identification requires learning something about the system and how it operates over periods of time. For the clinical investigator in the process of learning, the multiple factorial description of process is well nigh essential.

The early and famous "personality profiles" [3] (believed by their proponent characteristic of certain diseases or syndromes) have given place today to formulation of characteristic nuclear conflicts. In addition to a greater detail in psychiatric delineation, the latter formulations place greater emphasis on long-term time sequences.

Faced with a given patient, how does one discover emotional and behavioral patterns which, in the course of the investigation, may become candidates for the status of psychosomatic specificity?

At one extreme stands the recommendation for a psychosomatic history which the proponent believed could be taken "with a little practice" in a period from fifteen minutes to a couple of hours [3]. Based on the psychoanalytically introduced technic of associative anamnesis [13], and exhibiting considerable variation with respect to "structuredness" or "open-endedness," this technic has had wide use both in the studies underlying "the personality profiles" and the more recent formulations.

\* cf. Pragmatism, J. W. Longmans Green & Co., New York, 1907, p. 171. Sputnik emphasizes that W. S. Franklin's pre-relativity view "the healthiest notion, even if a student does not wholly get it, is that physics is the science of the ways of taking hold of things and pushing them" (Science, Jan. 2, 1903) still has a measure of meaning in 1957.

At the other extreme stands the process of psychoanalysis, whose length and timing is a function both of the problems of the patient and of the training, geography and attitudes of the analyst.

Sometimes alone, \* more often in combination with interview technics, the projective tests of the psychologist are taking increasing prominence.

As the results of studies have appeared in increasing profusion, several skeptical questions have become prominent in the medical community. The most banal is this: Why is it that one may find a "characteristic" profile and/or nuclear conflict in many a patient who does not exhibit the disease for which the psychodynamic pattern is characteristic?

The parallelism to the finding of pathogenic organisms in the healthy is obvious: The question does not automatically eliminate possible pathogenetic significance for the psychodynamic pattern. It does emphasize the importance of elucidating other factors in a complex pathogenesis. To this end, long-term longitudinal studies become important. At their most fruitful, these may include genetic, physiologic, and biochemical variables as well as psychodynamic evaluation of the significance of events in the patient's continuing life history. An example is the ongoing long-term follow-up of individuals with high blood pepsinogen levels in childhood † (an age in which clinical evidence of peptic ulceration, although not unknown, is rare).

A second question implies a more serious prognosis for psychosomatic specificity and is frequently posed by physicians with great clinical experience in psychiatry: Why is it that, the longer and more intensively one works with a patient, the oftener one finds many or all of the supposedly characteristic psychodynamic patterns in a single individual who may or may not manifest psychosomatic disease?

Again the analogy to the multiplicity of the human body's bacteriologic flora in health and disease is obvious. Every comprehensive text-book of bacteriology is in part a scientific grave-yard for microorganisms accessible to culture when filtrable viruses were not. While not expecting the growth of a nuclear conflict in pure culture, this question reflects a genuine suspicion

<sup>\*</sup> cf., for example, the scoring of the Rorschach in terms of "body image" for correlation with psychosomatic symptom choice [14].

<sup>†</sup> Mirsky, I. A. Personal communication (see also [15]).

that a psychodynamic pattern might achieve the aura of psychosomatic specificity because it is the first and the easiest for the patient to talk about

An answer unique for its susceptibility to experimental validation has recently been put forward by a team whose specificity hypotheses have been based in the main on their own psychoanalytic studies. The answer, in essence, is this: Choose a group of patients representing seven diagnostic categories commonly termed psychosomatic. Show us a skillfully taken associative anamnesis on each patient's life story censored for any ordinary medical clues suggesting the "somatic" symptomatology. We can tell you what diagnoses do not apply to the patient and can probably name, with an accuracy far greater than expected from chance, the correct somatic diagnosis.

The design of the resultant study (as yet reported only in a preliminary fashion\*) warrants comment in exemplification of a determination on the part of a team of psychoanalysts to bring rigorous validation methods to bear on hypotheses emerging from use of psychoanalysis as a research instrument. The patients are selected by the diagnostic criteria accepted at four teaching hospitals in the area. The taperecorded associative anamneses are taken by a psychoanalytic team member with a rigidity aimed at exclusion of potential clues embodied in the variations of order, wording and emphasis of questions. The typed anamnesis is then censored for these and ordinary medical clues by an internist familiar with the psychosomatic hypotheses under investigation. The censored version is distributed for private diagnostic appraisal to: (a) the group of analysts (excluding the interviewer); (b) to a control group of mature internists selected for unfamiliarity both with psychoanalysis and psychosomatic hypotheses.

Each psychoanalyst brings his written formulation of the "nuclear conflict" together with the implied somatic diagnosis to the weekly research meeting at which the interviewing analyst sits, Beckmesser-like, behind a screen.

The group then seeks to reconcile individual psychodynamic appraisals in a joint formulation. If successful, this and the implied somatic diagnosis are recorded, and the interviewer emerges from behind the screen and divulges the correct somatic diagnosis. If psychodynamic evidence in the first interview is deemed insufficient by the group, the correct diagnosis is not divulged; the interviewer is instructed to explore, in one or more further interviews, areas believed inadequately covered in the first. With this information, properly censored, in the psychoanalyst's hands, the appraisal is repeated and the results are submitted to a statistician of a local university for comparison with the results of a comparable appraisal procedure by the "control group" of internists.

While comparison between diagnostic scores of psychoanalytic and control groups is not yet available for enough cases to have a bearing on the validity of the hypotheses of specificity, the study has already proved fruitful in several ways. In its pilot phases, the psychoanalytic diagnoses were far from uniformly correct, and for a brief period the internists were more often correct than might be expected from chance alone. In addition to bringing about continuous evaluation of such factors as structuredness and censorship of interviews (important to avoid "contamination") it brought about, notably in postmortem discussions of psychoanalytic diagnostic failures, a continuous sharpening of hypotheses. At the same time, the methodological problems of "weighting" psychodynamic information in a valid and reproducible fashion were inexorably highlighted, and the help of quantitatively minded psychologists was sought toward their solution.

#### THE RELIABLE IDENTIFICATION OF THE ORGANISM

#### The Problem of Consensus in Appraisal of Psychodynamic Data

One of the healthiest signs for the scientific future of psychosomatic relationships is the widespread appreciation of this problem among psychoanalysts today. As it emerges here, it is more immediate than the problem of divergences in theoretical formulation by the several "schools" of psychoanalysis. It is the problem of obtaining interpretive agreement by a single

motions of the late and impassive faced pathologist, Dr. S. B. Wollbach, at Peter Bent Brigham clinicopathological conferences).

<sup>\*</sup> A preliminary report of this study was given at the December meeting of the American Psychoanalytic Association, 1954 [16]. A progress report is to be delivered to the New York Academy of Medicine this fall (Alexander, F. Personal communication).

<sup>†</sup> Lest he divulge by involuntary expression how well or badly his colleagues are doing (vide, the telltale ear

group of workers, in daily intercommunication in a single institute, on the same data.\*

Clearly interpretive consensus does not guarantee interpretive correctness.

Some continue to maintain that psychoanalytic interpretations are not adaptable to a requirement of consensus.† One hears mention of the indisputable existence in the less personal areas of medicine, of the person who, over and over again, seizes on an apparently minor sequence of signs, symptoms and laboratory findings, and in so doing predicts future events in a fashion more accurate than his colleagues; at this level of psychiatric thought and observation psychoanalysis was born, and the internal consistency of an analyst's formulations are properly subject only to the requirements of predictive validation in the individual case.

Few will doubt that for the exploratory phases of a problem the unusually gifted observer is essential; internal consistency and predictive validation must be among his standards.

But without consensus in identification of

\* Many centuries were required for the geometrician and physicist to work out the implications for an area of knowledge far less emotionally charged than psychodynamics. The following marvelously compressed paragraph of Rougier, in giving the history for geometric interpretation, indicates certain logical implications for

the future of psychodynamic interpretation:

"It will turn out that the discovery of non-Euclidean geometry has been the origin of a considerable revolution in the theory of knowledge and, hence, in our metaphysical conceptions about man and the Universe. One can say, briefly, that this discovery has succeeded in breaking up the dilemma within which epistemology has been locked by the claims of traditional logic: the principles of science are either apodictic truth (logical conclusions synthetic a priori) or assertoric truth (facts of sense observation). Poincaré, taking his inspiration from the work of Lobatchevski and Riemann, pointed out in the particularly significant case of geometry that another solution is possible: the principles may be simple arbitrary conventions. . . . However, far from being independent of our minds and nature, they exist only by a tacit agreement of all minds and depend strictly upon the factual external conditions in the environment in which we happen to live." (ROUGIER, L. The Geometrical Philosophy of Henri Poincaré, Paris, 1920, as quoted in

† Psychoanalysis is not the only area for discovery in emotional realms where immediate consensus has carried suspicion of sterility. Robert Schumann, in writing of the "spiritual discoveries" he expected from the young Brahms, predicted without contemporary consensus but with an ultimate consensual validation that might be hard to achieve solely through the mastering of a recent and scholarly treatise which relates such "spiritual discoveries" to modern learning theory [18].

organisms where is the microbiology laboratory of today's hospital? Without consensus in over-all appraisal as a *goal* in the teamwork of today's medical, surgical and pediatric services, where is the day-to-day across the board effectiveness?

Thus to the physician in a general hospital it is particularly gratifying that, in the study mentioned in the last section, the concern of the psychoanalytic group occasioned by a failure of consensus in their psychodynamic formulations of a patient has been fully as great as that occasioned by a failure to name the correct somatic diagnosis.

There are aspects of assessment psychodynamic evidence which make the consensus of experts particularly reassuring to the physician who is not an expert. Let us take, by way of example the mechanism of denial, i.e., when an emotional configuration is not found by the examination used, its apparent absence may be weighted as of equivalent or stronger significance than if it had been found.

Thus, among a recently studied group of sad, object-deprived patients with reticuloendothelial disease, is a patient who felt "her job a challenge and an honor," who "emphasized how much she enjoyed her work, how well she did and how she could 'take it'." The authors go on to state "it was our impression that much of the patient's professed pleasure represented denial . . . that this role for the girl was a source of psychological dissolution even though more specific genetic or dynamic evidence was not elicited and there were no losses or separations of the type described for in the rest of the patients."\*

Bookkeeping wherein to be in the red and to be in the black has a comparable meaning is precisely what patient Strepsiades sought from therapist Socrates in the "Clouds." This is what Aristophanes laughed at in the dialogue between the just and unjust logics, † and it still can make a hardheaded physician uncomfortable.

Yet even a hardheaded physician with a bent for detached introspection can identify the mechanism of denial in his own everyday acts, e.g., in the personal facing of danger either from

\* See Greene, W. A., Jr., Young, L. E. and Swisher, S. N. Psychological factors and reticuloendothelial disease. II. Observations on a group of women and lymphomas and leukemias. Presented in part at the Annual Meeting, American Psychosomatic Society, 1955. See also [19].

† Aristophanes. The Clouds. (Translated by Rogers, B. B.) pp. 287, 311, 331, 337. Cambridge, 1950. Harvard University Press.

the external environment or internal disease.\* While qualitatively detectable, no amount of solitary introspection can evaluate the weight this common psychodynamic defense carries in one's daily affairs; indeed the greater the weight, the greater the likelihood of its introspective underestimate.

This is true for many of the other non-logical defenses in the interpersonal relationships of crucial import to the psychosomaticist. As yet only psychoanalytic methods [20] have yielded any approach to an estimate of "weight" or quantitative significance. By reason of the nature of the methods and their data, quantitation is still of the crudest sort. † Validation still must come in the main through verification of predictions in terms of psychoanalytically oriented observation. This type of observation is one of the most time consuming and expensive the psychosomaticist has, particularly when combined with contemporaneous measurement of physiologic and biochemical parameters. Both the promise and the labor in such work may be appraised in many ongoing studies ranging from infancy [21] to adulthood. ‡

In working with larger numbers of patients, this scale of study is unwieldy if not impossible. A critical question facing many a psychosomatic worker today is this: At what point does one lose hope of validation in curtailing intensiveness and extensiveness of the psychodynamic study?

The answer is not yet at hand. In part it must come from the projective technics of the

\* The former has been celebrated by the modern comic poet, W. S. Gilbert, in the introspective song of the policemen about to do battle with the redoubtable Pirates of Penzance:

Though in body and in mind— We are timidly inclined— And anything but blind— To the danger that's behind—

Yet when the danger's near—We manage to appear—As insensible to fear—As anybody here—AS ANYBODY HERE, etc., etc.

† Indices of autonomic function, the various hormones of the adrenal gland, circulating enzyme levels have not yet refined the quantitation. Despite great labor in the last ten years, no group of physiologic or biochemical parameters appear to supplant the clinical gauge of the magnitude of an individual's anxiety through an appraisal of the operation of his defenses against it.

‡ e.g., the studies of asthma under way at Boston University [22].

psychology (which have always had the merit of cross validation by independent scorers). In part it must come from the scrutiny of the psychoanalytically oriented interview. Consensus of independent observers, while no guarantee, will probably prove necessary for correctness in the scrutiny.

It is easy to see why this has been slow to come about for psychoanalytically obtained data. The relationship of psychiatrist and patient has stressed and should stress complete confidentiality of content. Many workers have feared both distortion of data as well as interference with therapy might result from violation of this privacy in the interest of scientific method. Genuine doubts have accompanied the introduction and slowed the utilization of nearly every device lending itself to joint study, from the simple wire recorder and the one way screen to a continuous sound and cinematographic recording [23]. A similar concern has accompanied the introduction of simultaneous physiological and pharmacologic measurements to the diadic therapeutic situation [24].

An increasing experience has in great measure allayed this concern through indication of the areas in which distortion and/or interference with the patient-therapist relationship may or may not be expected.

### THE CRITERIA FOR IDENTIFICATION OF THE ORGANISM

#### The Dynamics of Psychoanalytic Theory

The originator of psychoanalysis differed from Aristophanes, among other ways, in this: a life dedicated to the use of "the just logic" to study the behavioral characteristics of "the unjust logic," rather than to laugh at it.

The resultant young body of theory (in addition to a capacity to arouse emotion equal to the greatest of the revolutionaries among scientific theories) has been suspected of even greater capacity to inhibit further elucidation at the hands of the very workers who passed existing frontiers thereby. This is reflected in a question attributed to a distinguished contemporary physiologist: Why is it that of Einstein and Freud (whose first revolutionary publications were nearly simultaneous), theories of the former have been subject to revisions and extensions almost as revolutionary as their origins, while the theories of the latter are maintained in some

institutes in the static state prerequisite to sacred literature?

The hardheaded physician (who has no trouble with accepting biologic fact of "unjust logic" in the structure of psychodynamic defenses but wants just logic in appraisal of their psychosomatic significances) will feel encouraged that many of his colleagues in psychoanalysis are intensively concerned with the same matters as related to mental illness.

A psychoanalyst known for his broad scientific as well as research and clinical capacity has thus characterized [25] psychoanalytic theory of the 1950's: (1)"A mixture of propositional concepts, explanatory concepts, hypothetical constructs, inferences and many other necessary tools of good scientific theory, but here not sufficiently differentiated as to their nature and their degree of existential probability; (2) freely used metaphors, analogies and similes, which have undoubted didactic and hence potential heuristic value, but only obfuscate the theoretical issues; and (3) a good bit of pure speculation." The ongoing work of clarification, elaboration and verification seems likely to bring into the body of psychoanalytic theory the operational logic so eloquently elucidated for the physical sciences by the physicist Bridgman [26].

In this connection another quotation from the same psychoanalyst [25] is worth setting beside the first: "... since for Freud the therapeutic goal was for a long time identical with maximal historical reconstruction, no distortion of the research method was involved. With this method he was able to make a series of unique observations which have subsequently been repeated thousands of times by other observers using the same method. If these direct observations can in fact be made by this method only, which is true, in my opinion, for some but by no means for all of the basic data of psychoanalysis ... it is entirely justified to demand that the

\*The somewhat distorted essence of Bridgman's thought is this: that as a theoretical concept moves from heuristic to expository status, the degrees of freedom of its logical components should narrow to the degrees of freedom of the operations involved in its existential verification.

On this basis, it has been well said that "the existential probability of such concepts as the unconscious or repression is just about as high as that of the physical concept of matter, to judge by the same criteria of evidence" [25]. But this is hardly equivalent to saying that any particular statement of these concepts has high existential probability, any more than the mere existential probability of "physical matter" favors a particular physical theory.

method itself be examined carefully for possible techniques which could increase its relative objectivity and accessibility to critical scrutiny without sacrificing its unique heuristic qualities."

The hardheaded physician, if he reads the original treatise on dreams [27] side by side with that of a contemporary psychoanalytic researcher [28], cannot escape the trend from heuristic gift (tempered only by an internal critique) to the rigor of a scientific logician.

In many ways the road is harder than for the physical scientist. When one considers (even in a study of modest design) the shelf after shelf loaded with tape recordings of interviews and the reams of resultant transcriptions; the number of hours spent by psychoanalysts and psychologists in selection and semantic definition of variables subject to prediction and in devising scales to weight these; the number of hours spent in inevitable revisions after pilot codification of the first transcripts, one can stand appalled at the labor involved in certain of today's more elaborate studies (i.e., the cinematographic-sound study [23]).

THE PRODUCTION OF THE DISEASE IN A SUSCEPTIBLE ANIMAL SPECIES BY THE SPECIFIC MICROORGANISM

Experimental Neurosis, Psychosis and Psychosomatic Disease

In the history of microbiologic pathogeneses the third postulate of Koch has often had to be honored in the breach by reason of unsusceptibility of animals.

For the dynamic psychiatrist the value of animal evidence on the pathogenesis of human mental disease has had in recent years an increasing significance.

Common to diverse schools of dynamic psychiatry has been a postulate of comparable appeal to the stirring political message of our Declaration of Independence.\* No genealogical pedigree, no constitutional inadequacy, can deprive the individual of a right to mental health. The precipitating factors are considered in the main the individual's life experiences and his responses thereto, with only such emphasis on inborn abilities or lack of them as everyday experience makes inevitable. In this framework schizophrenia has been suggested as an "ultima thule of reactions to stress," and the broadening

\* For a more extended discussion of this point see p. 7 in [29].

of psychodynamics to a generalized science of biodynamics "whose theory must cover the whole range of behavior from ameba to man" has been envisaged [30].

The sparse therapeutic results of dynamic psychiatry in what Sullivan called "the patterns of difficulty" [31] (notably the psychoses), in part explains a prevalent longing for a pathogenetic Denkmittel\* in such areas as the newer discoveries in the neurophysiology of the reticular substance and the limbic systems, or the metabolic degradation patterns of serotonin. A memorable example is a recent Academic Lecture to the Annual Meeting of the American Psychiatric Association [32]. For the psychoses its theme can be best distilled from a footnote: "the demonstration of a chemical factor in the causation of schizophrenia would not help us to understand the contents of schizophrenic delusions-; it would merely make them superfluous."†

It is not difficult to understand the boost to psychodynamic spirits occasioned by reports of behavior resembling that seen by the psychiatrist in the office and hospital produced by purely behavioral technics in animals as different as sheep [35] and primates [36].‡

\* Such a Denkmittel does not necessarily imply (although it is usually accompanied by) a "reductionism" in systematic description. For a succinct discussion of the logical errors in reductionism vide pp. 2-3, [29].

† In this connection the type of clinical result associated with the work of such gifted and lifelong students of schizophrenic communication as the late F. Fromm-Reichmann [33] is worth mention. Certainly whether therapeutic successes were based on an insight not readily communicated cannot be now determined. There is little question that the method used demands a skill and an intensity of staff [34] effort incompatible with state hospital treatment of schizophrenia today. However, that "psychotherapy is not likely to relieve our overcrowding significantly" [32] has no relevance at all to the validity, partial validity or invalidity of pyschodynamic hypotheses of schizophrenia.

‡ While there have been some problems of reproduction of results between various laboratories, an emphasis on species differences and a precision in definition of technics would seem to show a great part of the work on experimental neurosis as solidly grounded.

An amusing and valid warning on interpretation has been hinted thus "the two year old girl who—seeing a litter of puppies suckling a bitch, ran to her mother shrieking 'Come quick, the puppies are eating up Bonnie,' told us a good deal about her fantasies—not very much about the puppies." ([26], p. 146.)

The similarities to human mental illness (ranging from "nervousness" to evidence of hallucination) clearly do not establish comparable pathogenetic significances for man, however they do not seem to make it wise to

Many "psychosomatic" phenomena have been encountered in this work with animals. While these phenomena resemble the tachycardias, the bowel hypermotilities, etc. that the physician sees in the office and general hospital, there has been little found that suggests specific relationships between the precipitating behavioral situations and the patterns of psychosomatic response. The clamp on the renal artery still has the advantage over motivational conflict with outward action blocked as a reliable method of inducing a sustained animal hypertension.

Very recently, however, there has appeared some evidence for a possible breakthrough for psychosomatic specificity on the animal level.

A strictly behavioral situation is presently under preliminary study, which, in certain primates appears to give rise to fatal peptic ulcer in well over three quarters of the animals studied.\*

If the preliminary observations are confirmed, how can relevance to human peptic ulceration be validated?

Clearly, it is impractical in man to duplicate (with proper biologic controls) the pathogenetic animal situation. However, if one can make a broad interpretation of what the animal situation might mean to man, one can (without recourse to any but commonplace language) describe many analogous situations into which man can get himself. Likewise, analogies can be seen with the psychodynamically phrased nuclear conflict that psychoanalysts have proposed for ulcer (although the pathogenetic situation was designed for an entirely different long term study whose completion the ulcers have in the main prevented).

This setback has provided an opportunity to document on an animal level matters difficult to accomplish in man: e.g., the relationship of genetic background and types of pre-experimental animal farm experience to susceptibility, and the possible roles of neurophysiologic and humoral pathways in the linkage between the behavioral situation and the eroded bowel. A multidisciplinary team is obviously involved.

As the data emerge it may be possible to

neglect the possibility in the interest of a new "reductionism." (vide, again, [29].)

\* Through the kindness of Drs. John W. Mason and David McK. Rioch of Washington, D. C., the writer has recently had opportunity to see the pathogenetic situation in operation in the laboratory [37].

describe the ulcer in terms of those conditions necessary and those combinations of conditions sufficient for the appearance and timing of disease manifestations.

#### SOME TENTATIVE CONCLUSIONS

Borrowed from a formalism of mathematical proof and recently urged for the clarification of psychodynamic pathogenetic significance [25], the specification of necessary and sufficient conditions is free of the philosophical objections to linear causality and is yet capable of indicating areas of value for therapeutic intervention for which the physician usually employs the word cause. With respect to psychosomatic enquiry there is no a priori limitation to the organizational level for which conditions may require specification: genetic, biochemical, neurophysiologic and psychodynamic may prove in the long run too brief a list.

At present, and despite many suggestive leads, there is no conclusive evidence that a specific psychodynamic pattern is either a sufficient condition or a necessary condition in the pathogenesis of any clinical entity commonly called psychosomatic.

Through the ongoing and active working out of existing leads there is emerging a sharpening of both psychodynamic observations and formulations; thus the psychodynamic aspects of psychosomatic studies are approaching the critique and precision expected of good clinical research on the biochemical and physiologic aspects.

This sharpening is occurring at a very considerable expense of methodologic thought and labor, both past and future. How much of this can be obviated without sacrifice of the chance for validity is a problem that faces anyone designing a psychosomatic study today. Answers in part may come from the use of psychoanalytically based technics both as tools and as objects of intensive research.

From the standpoint of the physician working in his office or in the general hospital, it is perfectly clear that every patient with peptic ulcer, essential hypertension, asthma, ulcerative colitis, etc. cannot have psychoanalytically oriented therapy. It is far from clear that even were the army of analysts available, that this would be routinely advantageous.

It is becoming clearer that events of daily living beyond being related to the ups and downs of the "psychosomatic" diseases are related in a fashion which to a greater or lesser extent is characteristic of the particular diagnostic category.

Therefore, a knowledge of existing hypotheses on psychosomatic specificity can be of real advantage to the doctor who takes the patient as his responsibility, even though the psychiatric aspect of his therapy may be limited to advice on job, work and leisure activities, eating, sleeping and aspects of his interpersonal life which are expressible in commonplace terms.

When listening to a patient's story and relevant to weighing one's advisory policy, it may sometimes emerge that problems in interpersonal relationships may play a role far more detrimental to the patient's everyday functioning than does the evidence of his psychosomatic disease.\*

Patients in this category probably stand in greatest need of skillful psychiatric help. Where available, and when feasible, great assistance can be had in joint medical-surgical and psychiatric management. Here the experienced psychiatrist can be as much aid in prognosis† as in day-to-day, week-to-week, year-to-year management. Simple cure from psychotherapy can rarely be expected; many a "psychosomatic" condition has outlived years of continuous psychoanalysis.

But an important and sometimes indispensable role in palliation can be validated from clinical experience.

When skilled psychiatric help is not available, the doctor may undertake to substitute but in so doing he should stay the simply human doctor and not play psychiatrist. I start those of my house staff who seem to have a bent for this sort of work, not with the detail of specificity hypotheses, but with the reading of a single book [33], chosen for four reasons: (1) because it is short; (2) because it contains a minimum of unvalidated theory; (3) because it graphically depicts the potential discomforts of the doctors, young and old, in therapeutic relationships they do not fully understand; and (4) because its

<sup>\*</sup> Such listening is best taken in stages, sandwiched in with the ordinary enquiries dealing with other aspects of the patient's problem. As an experienced worker of psychosomatics is reputed to say to his students "If the patient takes you for a psychiatrist at this stage, you flunk." [38].

<sup>†</sup> In addition to the natural history of psychosomatic diseases, the psychiatrist has other areas of natural history to lean on (vide Sullivan's description of prognostic thinking in an acute schizophrenic break; [31], p. 195 et seq.).

emphasis is on the value of listening and the harms of premature interpretation. The greatest of these is listening, and by this, after all, are specificity hypotheses going to be judged in the individual daily practice of medicine.

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# The Natural History of Postnecrotic Cirrhosis\*

A Study of 221 Autopsy Cases

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Postnecrotic cirrhosis has been recognized as pathologic entity for several decades [1] but it is probably the least well studied of the various morphologic types of cirrhosis. Among the reasons for a lack of attention has been its uncommon occurrence, a need for pathologic confirmation before it can be differentiated from other, more clinically apparent types of cirrhosis, and a reluctance on the part of many clinical workers to accept it as a true cirrhosis [2,3]. It has recently been noted that the incidence of postnecrotic cirrhosis has markedly increased among autopsy cases at this hospital during the years 1947 to 1954 [4,5], and that postnecrotic cirrhosis predisposes to primary hepatic carcinoma with much greater frequency than other types of cirrhosis [4-7]. The present study was therefore undertaken to investigate these observations further and to study the natural history of the disease. An analysis has been made of the clinical, laboratory and pathologic features of 221 cases in which autopsy has been performed at the Boston City Hospital during the years 1917 to 1956.

#### REVIEW

Terminology. Many terms have been used to denote postnecrotic cirrhosis, the earliest of which was probably "multiple nodular hyperplasia," used by Felix Marchand, a German pathologist, in 1895 [8]. Mallory, who in 1911 first accurately characterized the pathologic features and distinguished it from other types of cirrhosis, referred to it as a "toxic" cirrhosis [1], although he later adopted the term "healed acute yellow atrophy" [9]. Karsner [10] is usually

credited with proposing the name postnecrotic cirrhosis, which is widely used at the present time. Other terms have included "coarse nodular cirrhosis" [11], "posthepatitis cirrhosis" [12], and "postnecrotic scarring" [10].

Relation to Acute Yellow Atrophy. The etiology of postnecrotic cirrhosis is far from clear at the present time; it is often considered to follow an acute injury to the liver, in contrast to a chronic progressive injury such as occurs in patients with chronic alcoholism and poor nutrition [11]. According to this concept, if a patient does not die of acute yellow atrophy of the liver, but instead recovers, a healed acute atrophy or postnecrotic cirrhosis may result [1]. It is still a matter of some controversy whether or not viral hepatitis, which may cause an acute necrosis of the liver, may lead to postnecrotic cirrhosis. The earliest cases of acute yellow atrophy were probably recorded by Baillou, who died in 1616 [13], and the term was proposed by Rokitansky [14], who described the pathologic changes. Frerichs [15] emphasized the clinical features and summarized most cases up to 1857. Following early descriptions and a general recognition of the condition of acute yellow atrophy, the question arose as to whether or not it could occur in a healed state. Up to 1908 approximately thirty cases of recovery were recorded, but such recovery was not fully accepted until McDonald and Milne [16] gave extensive descriptions of five cases in healing stages, and until Umber [17] reported a carefully documented case of recovery.

Etiology. Three possible etiologic factors have received particular attention in postnecrotic

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cirrhosis. The first has been the relationship between viral hepatitis and postnecrotic cirrhosis. Observations concerning the role of viral hepatitis in causing cirrhosis in man might arbitrarily be grouped under three headings: (1) those studies in which there have been chiefly clinical observations [18-25]; (2) those in which information has been obtained from autopsies [26-32]; and (3) biopsy studies in which patients with viral hepatitis have been followed up for periods of months to years by means of histologic as well as clinical observations [12,33-42]. One limiting factor in reviewing the majority of these studies has been the failure of most workers to distinguish cirrhosis of the postnecrotic type from other morphologic types of cirrhosis. From autopsy studies it has not been possible to establish the conditions giving rise to cirrhosis, and many possible factors have often been present, such as alcoholism, cholelithiasis and viral hepatitis [31]. Probably the best evidence to date that cirrhosis occurs as a result of viral hepatitis comes from studies in which patients with known hepatitis have been followed up for long periods of time with clinical observations and hepatic biopsies. Roholm and Iverson [40] in 1939 were the first to carry out such studies.

The second etiologic factor of interest has been hepatic toxins such as carbon tetrachloride, but there is very little evidence to implicate toxins in most cases of cirrhosis in man. A coarse nodular cirrhosis can be produced in experimental animals using agents such as carbon tetrachloride [43], selenium [44] and chlorinated hydrocarbons [45,46], but a portal type of cirrhosis is produced with most agents [47,48], and varying types of liver damage are produced with others, most of which appear to bear little resemblance to postnecrotic cirrhosis in man [49-62].

The third etiologic factor of interest has been dietary deficiencies. Himsworth and Glynn [63-65] popularized the concept that protein deficiency may be of importance in cirrhosis of the postnecrotic type, although caution has been expressed concerning the applicability of experimental work in animals to hepatic necrosis in man [66,67]. The earlier work leading to the concepts of Himsworth and Glynn, and subsequent experiments that have added to our knowledge of experimental liver disease, have been well reviewed by Beveridge [66], Hartroft [67], and in publications of a conference on nutritional factors and liver disease [68].

#### MATERIALS AND METHODS

The present study deals with 221 cases of postnecrotic cirrhosis in which autopsy was performed at the Mallory Institute of Pathology during the years 1917 to 1956. Cases were found by means of a systematic search of autopsy protocols [4,5]; these were studied and abstracted. Microscopic sections of the liver from all subjects were reviewed, and in this way twelve equivocal cases were excluded from consideration. In addition, stored liver tissue that had been fixed in Zenker's solution was obtained in nearly every case, and further sections were prepared and stained with phloxine methylene blue, Mallory's aniline blue stain for connective tissue, and a modification of Bielschowsky's silver stain for reticulum. Stored microscopic sections of kidney, heart, pancreas and other organs were reviewed in cases in which the diagnostic findings had been indefinite or equivocal.

The 221 cases of postnecrotic cirrhosis were analyzed as one group and as three subgroups. The subgroups were as follows: thirty-one patients with primary hepatic carcinoma in addition to postnecrotic cirrhosis, twenty-six patients with fatty nutritional (alcoholic) cirrhosis in addition to postnecrotic cirrhosis, and 164 patients with postnecrotic cirrhosis without either hepatic carcinoma or fatty nutritional cirrhosis. Of the 221 patients, the clinical records of 168 were available for review. These consisted of twenty-five of the thirty-one patients with primary hepatic carcinoma and postnecrotic cirrhosis, twenty-two of the twenty-six patients with fatty nutritional cirrhosis in addition to postnecrotic cirrhosis, and 121 of the 164 patients with uncomplicated postnecrotic cirrhosis. Cases of acute and subacute atrophy were not included in the present study.

#### ANALYSIS OF PRESENT CASES

Age. Figure 1 illustrates the age by decades of the 221 patients in this study. The predominant age range was fifty to seventy-nine years; approximately 75 per cent of the patients were age fifty or more. The average age of all patients in the study was fifty-seven years. There was no significant age difference among Caucasians, Negroes and Chinese. As might be expected, the average age of patients during the most recent years, 1947 to 1956, was somewhat greater (sixty years) than in previous years, 1917 to

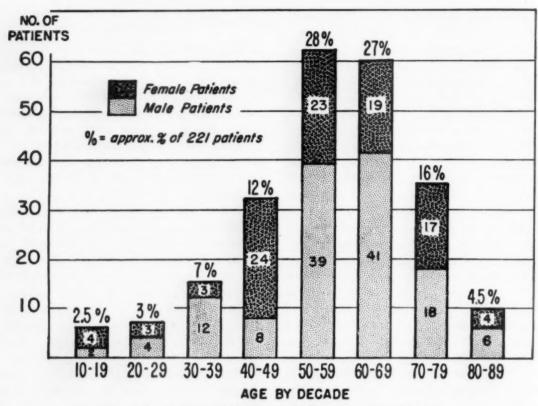


Fig. 1. Age and sex of 221 patients with postnecrotic cirrhosis.

1946 (fifty-eight years), but this increase was only slight, as pointed out in previous publications [4,5]. The average age of the patients with primary hepatic carcinoma was sixty years, slightly greater than that of patients with postnecrotic cirrhosis alone (fifty-eight years) and of patients who had fatty nutritional cirrhosis in addition to postnecrotic cirrhosis (fifty-two years). Despite recent increases in the occurrence of postnecrotic cirrhosis, the average age of patients was not significantly different from former years; the average age of 21,202 patients autopsied at this institute during the years 1917 to 1954, omitting infants and stillborns, was fifty-seven years. Similarly, the average age of all patients autopsied, excluding infants and stillborns, during the years 1947 to 1954 was sixty-three years, so that the average age at death of patients with postnecrotic cirrhosis was comparable to that of all patients at this institute.

Sex. As shown in Figure 1 the number of males (59 per cent) with postnecrotic cirrhosis outnumbered females (41 per cent); males outnumbered females at all ages with the exception of the decade forty to forty-nine years. Increases in postnecrotic cirrhosis during the recent years

were not related to an unusual number of cases in females. There were no cases of postnecrotic cirrhosis in Chinese females in this series. This is most probably related to the fact that of eighty-three autopsies performed on Chinese persons in 23,114 autopsies, only five were performed on Chinese females, and three of these were infants.

Race. Ninety-one per cent of the 221 patients in this study were Caucasians, 7 per cent were Negroes and 2 per cent were Chinese. The autopsy population of this institute is made up of comparable percentages of the three races with the exception that Chinese persons are rarely seen among autopsy cases. Ninety-one per cent of 23,114 autopsies over a thirty-eight-year period were performed on Caucasians, 8.7 per cent on Negroes, and 0.3 per cent on Chinese. The incidence of postnecrotic cirrhosis among Chinese was therefore greater than would be expected from their prevalence in the autopsy population.

The number of patients who were born in countries other than the United States was of interest. Information as to place of birth was available in 168 records of which fifty-nine patients (35 per cent) were foreign-born; all had

Table 1

MAJOR COMPLAINTS UPON ADMISSION TO HOSPITAL OF 168 PATIENTS WITH POSTNECROTIC CIRRHOSIS

	Complaints						
Data	Ascites (%)	Abdominal Pain (%)	Vomiting of Blood (%)	Stupor and Lethargy (%)	Jaundice (%)	Weakness and Weight Loss (%)	Other (%)
Total: 168 patients with post- necrotic cirrhosis	30	17	14	12	9	3	15
121 patients with postnecrotic cirrhosis only	28	12	15	14	10	0	21
carcinoma and postnecrotic cirrhosis	16	56	4	0	4	20	0
cirrhosis and postnecrotic	55	0	18	18	9	0	0

been in this country for at least ten years before death. In addition, the five Chinese patients were presumed to have been born outside the United States, but definite statements to this effect were not given with the records. Of the fifty-nine patients born abroad, twelve were born in Ireland, twelve in Italy, seven in Greece, five in Sweden, four in Canada, three each in England, Norway and Newfoundland, two each in Germany, Portugal and Lithuania, and one each in Poland, Bermuda and the Cape Verde Islands. Among twenty-five patients with primary hepatic carcinoma complicating postnecrotic cirrhosis thirteen (52 per cent) were foreign-born. Four were from Italy, four from Greece, and one each from Canada, Ireland, Sweden, Portugal and Cape Verde Islands.

#### CLINICAL DATA

Chief Complaint. The presenting complaints of 168 patients in this study are shown in Table 1. The most common complaint (30 per cent) was that of increasing or recent onset of ascites and edema; next (17 per cent) was that of abdominal pain, due for the most part to the occurrence of pain in patients with hepatic carcinoma; and third (14 per cent), was the complaint of vomiting of blood, generally of onset within a day of admission, and occurring without prodromal warning. Remaining complaints were stupor and lethargy progressing to hepatic coma (12 per cent), recent onset of jaundice (9 per cent),

weakness and weight loss (3 per cent) and miscellaneous complaints, generally not related to liver disease (15 per cent). Certain differences among the various groups were noteworthy. Ascites was most frequent in patients who also had fatty nutritional cirrhosis, while abdominal pain occurred in more than half of the patients with primary hepatic carcinoma, and was far less common in other groups. Although bleeding complications are more frequent among patients with hepatic carcinoma than in patients with cirrhosis alone [5], fewer patients with hepatic neoplasm sought hospital admission with initial complaints of vomiting of blood than was true of patients who did not have hepatic carcinoma. None of the patients with hepatic carcinoma presented with stupor and lethargy progressing to hepatic coma, a difference from the other groups, and the only patients with complaints of marked weight loss and weakness of such degree as to raise the question of neoplasm were those with hepatic carcinoma. Finally, a significant number of patients with uncomplicated postnecrotic cirrhosis presented with complaints unrelated to liver disease, such as infection, pneumonia and myocardial infarction. It may be inferred that in the majority of these patients cirrhosis was not symptomatic.

The pain in patients with hepatic carcinoma was chiefly abdominal, located in the right upper quadrant and the epigastrium. The character of the pain was usually described as crampy or

episodic, often with an additional steady dull upper abdominal ache. In these patients the duration of pain before admission ranged from two weeks to two years with an average of 4.8 months. Among those patients whose major complaint was pain, one-fourth also had marked ascites of recent onset.

Among 121 patients with uncomplicated postnecrotic cirrhosis the principal complaint on admission was increasing ascites and edema. The duration of ascites was one to one and a half years in four of thirty-four patients, but averaged only seven weeks in the remaining thirty patients. Fourteen patients (12 per cent) had abdominal pain as the chief complaint, but of these one-half had peritonitis, peptic ulcer or obstruction of the common bile duct.

Among twenty-two patients with fatty nutritional cirrhosis, the major presenting complaint was recent or severe and intractable ascites. In this group the average duration of ascites before admission was 4.4 months, with a range of two weeks to eighteen months. Of these patients five or 23 per cent had, in addition to other major complaints, some degree of abdominal pain. In only two patients was this upper abdominal or right upper quadrant pain; in the remaining three the pain was lower abdominal and crampy in character. One of these five patients had a bleeding peptic ulcer but in the remaining four there were no findings at autopsy to explain abdominal pain other than liver disease.

Duration of Illness. The length of time that patients were in poor health before admission to the hospital was of interest. Of 166 patients, 54 per cent had been ill less than six months, 11 per cent had been ill for a period of six months to one year, 15 per cent from one to two years, and 20 per cent more than two years. In summary, 65 per cent of the patients in this study were ill less than a year, and 80 per cent were ill less than two years.

Use of Alcohol. The clinical records of 146 patients contained definite information concerning the use of alcohol. Twenty-three per cent of these patients stated that they did not use alcohol in any amount, and the majority of such histories were borne out by information given during a previous admission, or by information obtained from family and friends. Eighteen per cent stated that they took only an occasional drink or no alcohol at all, 14 per cent used alcohol to a moderate degree, and 35 per cent were heavy and chronic users of alcohol. The

patients in this study thus might be divided into two large groups in regard to use of alcohol: 51 per cent either did not consume alcohol in any form or took only an occasional drink, while 49 per cent were moderate to heavy users of alcohol. When patients with hepatic carcinoma were compared with patients with uncomplicated postnecrotic cirrhosis, there were no significant differences regarding alcohol consumption. Differences in history of alcohol intake were found, however, in comparing patients who had coexistent fatty nutritional cirrhosis in addition to postnecrotic cirrhosis; the majority of such patients gave a history of excessive alcohol intake.

Nutrition. Of 108 patients with a definite statement in the record concerning nutrition, 63 per cent were said to have had adequate nutrition, which in general included meat in the diet and at least two meals per day. The remaining 37 per cent gave a history of poor dietary habits, often related to alcoholism. Poor dietary history was especially frequent among patients who also had fatty nutritional cirrhosis. Among nineteen patients with primary hepatic carcinoma, 37 per cent gave a poor dietary history.

Previous Jaundice and Hepatitis. Information related to previous hepatitis or jaundice was available from the clinical records of 168 patients, and from an additional twenty-two patients whose clinical histories and courses were briefly summarized in pathological protocols. Forty-five patients (24 per cent) had in the past had jaundice or an illness suggesting hepatitis. These cases are summarized in Table II. In many instances the interpretation of a previous disease such as hepatitis was made by the authors from a review of the clinical and epidemiologic features of the earlier disease. In 80 per cent of the forty-five patients the initial illness was accompanied by jaundice and in the remaining 20 per cent a definite statement of jaundice at the time of the illness was not recorded. The previous jaundice or hepatitis took place several years before death in most cases. The average period of time from an initial episode of jaundice until death with postnecrotic cirrhosis was thirteen years, excluding a single instance in which the interval was unusually long, seventy years. Thirty-three per cent of the forty-five patients had been receiving parenteral injections shortly before the onset of jaundice, and an additional 4 per cent became icteric during an outbreak of epidemic jaundice, in which persons of their

acquaintance had been similarly ill. The use of alcoholic beverages in the forty-five patients was approximately the same as in all patients in this study; 35 per cent stated that they did not consume alcohol in any amount, 25 per cent used alcohol in slight to moderate amount, and 40 per cent were consumers of alcohol to excess for several years. In approximately 9 per cent of cases the initial episode of jaundice was preceded by chronic intake of alcohol and the jaundice might have been related to the ingestion of alcohol. These cases are included, however, because it might also be speculated that in these patients alcohol intake complicated a viral hepatitis.

The forty-five patients could be considered in two groups according to the time interval from the initial episode of jaundice (presumably representing viral hepatitis) to the appearance of manifestations of continued or severe liver damage. Such manifestations were the appearance of ascites, recurring jaundice, recurring pain in the right upper quadrant of the abdomen, or a diagnosis of cirrhosis of the liver made during a subsequent hospital admission. The largest number, 62 per cent, was that in which an asymptomatic period of from three to seventy years, with an average of fifteen years, elapsed before the appearance of manifestations of continued or severe liver disease. Once these features became evident, 32 per cent of the twenty-eight patients survived two to eighteen years, with an average of six years, while 68 per cent survived an average of only two months. The second group, 38 per cent of the forty-five with previous jaundice or hepatitis, was that in which recurring jaundice, ascites or pain in the right upper quadrant developed within a year of the initial episode of jaundice, and nearly all these patients continued to have jaundice, ascites or pain at intervals until death. The average time from the initial episode to manifestations of continued liver damage was four months in thirteen of the seventeen patients, excluding here four patients in whom alcohol appeared to be a precipitating factor in the development of jaundice. In these thirteen patients the time elapsed from the onset of ascites or jaundice to death was seventeen months.

From the data it might be speculated that there are two courses followed by patients in whom cirrhosis develops after hepatitis. (Fig. 2.) Approximately two-thirds of patients have a long latent period averaging fifteen years before the onset of ascites, recurring jaundice or recurring pain in the right upper quadrant. Once these manifestations appear, two-thirds are dead in an average time of two months, while approximately a third of patients survive an average of six years. The second course is

Table II

PAST HISTORY OF HEPATITIS, JAUNDICE, SYPHILIS, MULTIPLE

PARENTERAL INJECTIONS AND SURGICAL PROCEDURES

AMONG 190 PATIENTS WITH POSTNECROTIC

CIRRHOSIS

Past History	Patients in Each Category (Per cent of 190 Patients)	Patients in Each Category (Omitting Duplications) (Per cent of 190 Patients)
Hepatitis or jaundice	24	24
Syphilis	23 14	17 11
therapy	9	6
therapy Previous surgical procedures	26	16
(at which time parenteral injections were given)	44	17
Total		- 74

followed by the remaining third of these patients. After the initial episode, evidence of continued or severe liver damage appears within approximately one year. Manifestations of liver damage in this group are then more or less continuous until death, and the average survival from onset of symptoms is only seventeen months.

Previous Antisyphilitic Therapy and Multiple Injections. A total of forty-three of the 190 patients (23 per cent) either had syphilis in the past or had serological syphilis at the time of their terminal admission. In seventeen of the forty-three patients there was no information concerning previous antisyphilitic therapy, in twenty-six there was a definite history of multiple injections during the course of such therapy. In only one instance was penicillin given; in all other cases treatment was with the heavy metals, chiefly arsenicals, bismuth and mercury. The time before death when therapy was admin-

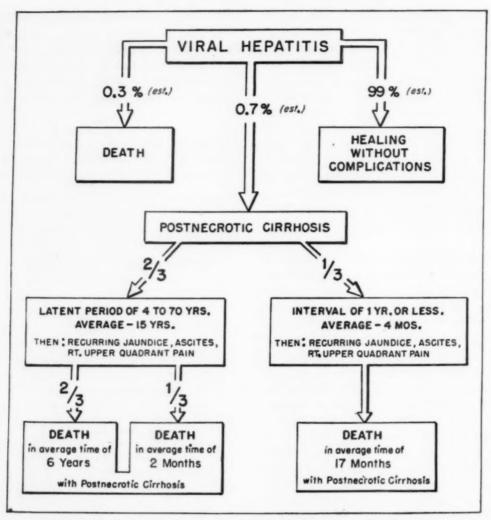


Fig. 2. Schematic concept of postnecrotic cirrhosis following viral hepatitis.

istered was generally several years; one patient had received therapy six months before death; in the remaining twenty-five patients the average time was twenty-six years prior to death, although of this number nine patients continued to receive courses of therapy for as long as twenty years after the initial treatment. Only five of the twenty-six patients gave a history of complications during antisyphilitic therapy; in three cases this was jaundice, in one case it was epigastric distress, and in one case it was an illness characterized by epigastric distress and an enlarging liver. Of the twenty-six patients six denied drinking alcohol in any form, seven stated that they took only occasional social drinks, and eleven were heavy users of alcohol for approximately twenty years before death; no history concerning alcohol intake was available in two patients. It appeared that only two patients had used alcohol to excess prior to

receiving antisyphilitic therapy, and the remaining nine heavy drinkers dated the onset of excesses from about the time when antisyphilitic therapy was given. Of the 190 patients fifty-nine (26 per cent) had received multiple injections other than as courses of therapy for syphilis. These were usually given during hospitalization in the form of mercurials, in giving British anti-lewisite (BAL) for Wilson's disease, and as various types of intramuscular and intravenous therapy. Eighty-three patients of the 190 (44 per cent) had undergone surgical procedures several years prior to death, at which time injections had been given. Chief among these procedures were appendectomy, hysterectomy and gastrectomy. In summary, as shown in Table II (in which duplications are excluded) 24 per cent of patients in this study had hepatitis or jaundice several years prior to death, and an additional 44 per cent had been at greater

than usual risk in regard to viral hepatitis in that they had received therapeutic or parenteral injections while in the hospital.

Relation between Diabetes Mellitus and Postnecrotic Cirrhosis. The relationship between diabetes mellitus and Laennec's cirrhosis has been a subject of controversy in the past [2,69-71]. In the present study there appeared to be an association between diabetes mellitus and postnecrotic cirrhosis and for this reason it is considered in some detail. Among autopsies, diabetes mellitus occurred with the same frequency in persons with cirrhosis as in persons who did not have cirrhosis. The converse was also true, that cirrhosis was of the same frequency in persons with diabetes mellitus as in persons who were not diabetic. However, there were differences when specific morphologic types of cirrhosis were considered. These are summarized in Table III, based on an analysis of 10,015 consecutive autopsies during the years 1945 to 1955. The incidence of clinically diagnosed diabetes mellitus was 4.8 per cent in 10,015 autopsies; among patients with cirrhosis it was approximately the same, 4.9 per cent, as in persons without cirrhosis, 4.7 per cent. As stated, the converse relationship was also true; among diabetic patients the incidence of cirrhosis was 13.8 per cent and in persons without diabetes it was 13.4 per cent. Three groups of patients with cirrhosis differed in this relationship; these were patients with postnecrotic cirrhosis, patients with fatty nutritional cirrhosis, and patients with hemochromatosis. Postnecrotic cirrhosis occurred in 2.5 per cent of persons with diabetes as compared with 1.3 per cent of persons without diabetes (X2:4.31), and hemochromatosis was found in 1.5 per cent of those with diabetes but in only 0.5 per cent of those without (X2:5.57). Fatty nutritional (alcoholic) cirrhosis was less frequent among diabetic patients, occurring in 4.2 per cent, compared with an incidence of 7.3 per cent among those without diabetes (X2:5.57). The latter is of interest because hepatomegaly due to fatty infiltration was slightly more common among diabetic patients (14.0 per cent) than among non-diabetic patients (10.6 per cent), although the difference was not statistically significant (X2:0.10). The remaining types of cirrhosis, biliary, cardiac and undetermined, occurred with approximately the same frequency in those with diabetes as in those without diabetes.

#### LABORATORY DETERMINATIONS

Hematologic Studies. Routine blood studies yielded few results of diagnostic importance. The average hematocrit value in 105 patients was 35 per cent. There was no significant difference in values upon comparing patients with

Table III

RELATIONSHIP OF CIRRHOSIS AND DIABETES MELLITUS IN

10,015 AUTOPSY CASES AT THE MALLORY INSTITUTE

OF PATHOLOGY, 1945 TO 1955

Type of Cirrhosis	Incidence of Cirrhosis in Diabetic Patients (%)	Incidence of Cirrhosis in Non-diabetic Patients (%)	Incidence of Diabetes Mel- litus in Persons with Cirrhosis (%)
Postnecrotic	2.5	1.3	9.0
Fatty nutritional	4.2	7.3	2.8
Hemochromatosis	1.5	0.5	13.0
Biliary	1.9	1.5	6.0
Cardiac	1.0	0.9	5.4
Undetermined	2.7	1.9	6.8
Totals	13.8	13.4	
Average			4.9
Fatty infiltration*	14.0	10.6	6.2

<sup>\*</sup> Although fatty infiltration of the liver is not a type of cirrhosis, the group is included here for comparison.

uncomplicated postnecrotic cirrhosis with those who also had primary hepatic carcinoma or fatty nutritional cirrhosis. In 101 patients the white blood cell count averaged 7,480 cells per cu. mm.; in 133 patients the average polymorphonuclear differential count was 77 per cent, and the lymphocyte differential count was 17 per cent. In sixty additional patients the white blood cell count was greater than 10,000 cells per cu. mm.; in all but three of these cases conditions were found at autopsy that were sufficient to explain the elevated white blood cell counts. The findings were infection-chiefly pneumonia, peritonitis and pyelonephritisbleeding esophageal varices, pancreatitis, acute myocardial infarction and pulmonary infarction. There was no evidence that patients with uncomplicated postnecrotic cirrhosis had elevated white blood cell counts due to liver disease and it may be inferred that an elevated white blood cell count in a patient with postnecrotic cirrhosis should lead to the suspicion of a complicating illness. The fasting blood sugar in forty-five patients, excluding those with known diabetes mellitus, averaged 104 mg. per cent; lower values were found in patients with superimposed hepatic carcinoma than in other pa-

Table IV

AVERAGE VALUES OF LIVER FUNCTION TESTS IN PATIENTS WITH POSTNECROTIC CIRRHOSIS

Laboratory Determination	Postne	ts with ecrotic hosis nly	Postn Cirrho He	nts with ecrotic osis and patic inoma	Postr Cirrh Fatty	nts with necrotic osis and Nutri- Cirrhosis	Postne	atients ith ecrotic rhosis
Bromsulphalein (BSP) (% retention)	(27)*	31	(11)	46	(8)	46	(46)	37
Prothrombin time (% of normal)	(42)	65	(17)	61	(12)	64	(71)	63
Cephalin flocculation test (% abnormal)	(49)	90	(16)	94	(15	100	(80)	93
Formol gel test (% abnormal)	(40)	58	(12)	83	(12)	50	(64)	61
Serum total protein (gm. %)	(64)	5.9	(18)	6.2	(12)	6.4	(94)	6.1
Serum albumin (gm. %)	(42)	2.8	(14)	2.9	(9)	2.2	(65)	2.7
Serum globulins (gm. %)	(42)	3.2	(14)	3.7	(9)	4.0	(65)	5.3
Serum alkaline phosphatase (Bodansky Units)	(24)	5.2	(9)	6.6	(4)	5.2	(37)	5.5

\* Figure in parentheses indicates the number of patients in whom the laboratory determinations were made.

tients with postnecrotic cirrhosis. Among eight patients with primary hepatic carcinoma the fasting blood sugars averaged 76 mg. per cent. Two values were 50 mg. per cent or less, and only one value was 100 mg. per cent or more. Among patients with associated fatty nutritional

Table v
WEIGHT OF THE LIVER AT AUTOPSY IN PATIENTS WITH
POSTNECROTIC CIRRHOSIS

POSTNEGROTIC CIRCHOSIS								
	Liver Weight (gm.)							
Group	<1,000 (%)	1,000- 1,500 (%)	1,501- 2,000 (%)	2,001- 2,500 (%)	>2,500			
159 Patients with post- necrotic cirrhosis only 26 Patients with postnecrotic	32	44	16	6	2			
cirrhosis and fatty nutri- tional cirrhosis	8	46	31	0	15			
cirrhosis and primary hepatic carcinoma	7	19	29	29	16			

cirrhosis, and patients with uncomplicated postnecrotic cirrhosis, the fasting blood sugar averaged 97 mg. per cent; only two were below 100 mg. per cent, and one of these was 60 mg. per cent with no apparent explanation from the findings at autopsy. The finding of low fasting blood sugar values in patients with primary hepatic carcinoma is of interest because of reported cases of spontaneous hypoglycemia [5], and because of studies showing that patients with hepatic carcinoma have altered glucose tolerance tests [72,73].

Liver Function Tests. Liver function tests are summarized in Table IV. There was little difference in tests among patients with primary hepatic carcinoma as compared with other patients with postnecrotic cirrhosis, with the exception of the alkaline phosphatase determination, which was slightly elevated (average of 6.6 Bodansky units) in patients with hepatic carcinoma. A feature of interest was that the average serum globulin value was only 3.5 gm. per cent in sixty-five patients with postnecrotic cirrhosis, a finding in contrast to many studies in which higher globulin values have been reported [31,37,74-79].

#### AUTOPSY FINDINGS

Liver. The size of the liver in postnecrotic cirrhosis was generally reduced, although the clinical findings of a palpable liver were very misleading in that 50 per cent of patients had had palpable livers, but in 15 per cent of cases with a palpable liver the hepatic weight was 950 gm. or less at autopsy. Patients with hepatic carcinoma frequently had a palpable liver (84 per cent), and the findings in this group generally correlated well with hepatomegaly at autopsy.

As shown in Table v, the weight was 1,500 gm. or less in 76 per cent of cases of uncomplicated postnecrotic cirrhosis. The addition of fatty nutritional cirrhosis or primary hepatic carcinoma to postnecrotic cirrhosis occasionally increased the size of the liver, but even with

these conditions the liver weighed 2,000 gm. or less in approximately 85 per cent of all cases. The color of the liver was described as yellow to gray in 56 per cent of 220 cases in which color was given; in 35 per cent the color was predominantly brown to tawny, and in 6 per cent the liver had a green color, generally associated with jaundice. As pointed out by Mallory [1] a yellow color was frequently found in nodules of regenerating liver tissue. In cases with tumor, the tumor nodules were most often a bright vellow to gray color and occasionally they were red-brown. Friability of tumor was especially noted in tumor that had invaded blood vessels. Nodularity of the liver was a prominent feature; the nodules were greater than 2 cm. in diameter in approximately 21 per cent of 215 cases. Intermediate sized nodules, ranging from 0.3 to 2.0 cm. in diameter, were found in 69 per cent of cases. In 10 per cent of cases the liver surface was described as granular, with nodules averaging approximately 0.1 to 0.2 cm. in diameter but in nearly all these cases there was superimposed fatty infiltration.

Spleen. Patients with uncomplicated postnecrotic cirrhosis had an average splenic weight of 358 gm., compared with a similar weight, 358 gm., in those with added primary hepatic carcinoma, and a larger size, 458 gm. in patients with added fatty nutritional cirrhosis.

Patients with varices generally had larger spleens than patients without varices, the difference in weights averaging approximately 100 gm. The weight of the spleen in patients with very small livers tended to be less than in patients with normal or large livers. The clinical detection of varices from the finding of a palpable spleen was of only limited use despite the occurrence of slightly larger spleens in patients with varices.

A satisfactory clinical examination of the spleen was recorded in 174 cases; the spleen was palpable in thirty-seven patients, of whom 68 per cent had esophageal varices at autopsy, while of the 137 patients who did not have a palpable spleen, varices were found in 53 per cent. Of ninety-eight patients with varices 26 per cent had a palpable spleen, and of sixty-six patients without varices nearly the same percentage, 18 per cent, had a palpable spleen.

Pancreas. Among 221 patients with postnecrotic cirrhosis, healed or active pancreatitis was found in 6 per cent of cases, compared with an incidence of 3 per cent in 20,399 autopsy cases at this institute, a difference that was not statistically significant.

Jaundice. Jaundice at the time of autopsy was slightly less frequent among patients with uncomplicated postnecrotic cirrhosis than in patients with superimposed fatty nutritional cirrhosis or primary hepatic carcinoma. Forty-five per cent of patients with uncomplicated postnecrotic cirrhosis had jaundice, compared with 68 per cent of patients with primary hepatic carcinoma and 77 per cent of patients with fatty nutritional cirrhosis.

Ascites. The frequency with which ascites occurred was greater in patients with fatty nutritional cirrhosis (88 per cent) and in patients with primary hepatic carcinoma (87 per cent) than in patients with uncomplicated postnecrotic cirrhosis (70 per cent). The quantity of ascites was less (average of 1.87 L.) in patients with hepatic carcinoma than in patients with uncomplicated postnecrotic cirrhosis (average of 2.95 L.), and it was greater in patients with added fatty nutritional cirrhosis (average 3.45 L.). There was no significant difference in the frequency or quantity of ascites in patients with varices as compared to patients without varices in each of the three groups. Bloody ascites occurred in 2.5 per cent of patients with uncomplicated postnecrotic cirrhosis (3.6 per cent of such patients with ascites), and in 23 per cent of patients with primary hepatic carcinoma (26 per cent of such patients with ascites); it did not occur in patients with fatty nutritional cirrhosis. This finding may be of help in detecting hepatic carcinoma. Only four patients without hepatic carcinoma had bloody ascites at autopsy and of these three had had paracenteses performed during the terminal admission, which may have caused intraperitoneal bleeding.

Esophageal Varices. Varices were found at autopsy in 115 of the 221 patients of this study (52 per cent). In one-half of these patients the varices were intact, the other half had bled during the terminal admission. (Table vi.) The patients with varices did not differ significantly as to age at death, presence or absence of jaundice, hepatomegaly, splenomegaly, or presence or absence of ascites from patients without varices. Melena was noted clinically in 33 per cent of patients with intact varices and in 71 per cent of those with bleeding varices, or in 52 per cent of the 100 patients. This probably indicated that many patients with intact varices at autopsy had had brief episodes of gastrointestinal bleed-

ing prior to death; a source of bleeding other than varices, usually peptic ulcer, was found in one-third of the patients who had had melena with intact varices at autopsy. In the remaining two-thirds the only demonstrable source of bleeding was esophageal varices. Liver function

Table VI ESOPHAGEAL VARICES AT AUTOPSY AMONG 221 PATIENTS WITH POSTNECROTIC CIRRHOSIS

Group	Intact Varices (%)	Bleed- ing Varices (%)	Total with Varices (%)
Total: 221 Patients 164 Patients with post-	26	26	52
necrotic cirrhosis only 31 Patients with post-	25	24	49
necrotic cirrhosis and primary hepatic carcinoma	23	29	52
necrotic cirrhosis and fatty nutritional cirrhosis	35	38	73

tests were not significantly different in patients with varices as compared with the values in patients without varices. Among patients whose varices were intact, 20 per cent had had a clinical diagnosis of esophageal varices prior to death; of the cases in which the diagnosis was made, two-thirds had had hematemesis or melena. Only one patient of the fifty-one with intact varices had had surgery for varices prior to death, in this case eight months before death because of hematemesis. An hepatic artery ligation had been performed and further bleeding did not occur; the patient died of acute peritonitis, apparently following repeated paracenteses for accumulating ascites. Surgical procedures for varices had previously been undertaken in eleven of the forty-nine patients who had bleeding varices at autopsy; in seven patients this surgery was performed during the terminal admission, and in four cases surgery had been performed eight months to four years prior to death. Of forty-nine patients who at autopsy had bleeding from esophageal varices, forty-four had died during their first hospital admission for bleeding.

Cholelithiasis. Among 212 patients, gall stones were found at autopsy in forty-nine cases (23

per cent); there was associated acute inflammation or ductal impaction in three instances. The frequency of occurrence among patients with uncomplicated postnecrotic cirrhosis was 23 per cent, among patients with primary hepatic carcinoma 27 per cent, and among patients with fatty nutritional cirrhosis 19 per cent.

Bleeding Tendency. At autopsy, a bleeding tendency, evidenced by purpura, hemorrhages into serosal and mucosal surfaces of the gastro-intestinal organs, epicardium of the heart, the lungs, bleeding from the gums, and endometrial bleeding, was found in twenty cases (9 per cent). In none of these twenty cases was there bloody ascites. From this it might be suggested that the cause of bloody ascites in patients with primary hepatic carcinoma was not a generalized bleeding tendency but was probably due to mechanical factors such as rupture of blood vessels invaded by tumor.

Causes of Death as Determined at Autopsy. Table vii summarizes the immediate causes of death as determined from clinical and autopsy review of 215 patients. The most common cause of death was infection (29 per cent) and it should be noted that "terminal" or slight bronchopneumonia and minor degrees of infection elsewhere were not adjudged to be sufficient to include as a cause of death. The next most frequent cause of death was bleeding (26 per cent), the source of which was esophageal varices in nearly all cases. Nine per cent of patients were considered to have died of liver failure.

Among the cases with death due to miscellaneous conditions (14 per cent) the chief findings were pulmonary infarction or atelectasis, immediate postoperative death, acute myocardial infarction, intracerebral hemorrhage and uremia. As had been noted in earlier publications [5], patients with primary hepatic carcinoma died of bleeding complications with greater frequency than patients with uncomplicated cirrhosis; this group also had less infection as a cause of death than patients with uncomplicated postnecrotic cirrhosis.

Infectious Diseases. Table VIII summarizes the occurrence of infectious disease in 220 patients with postnecrotic cirrhosis, excluding all cases in which a slight degree of bronchopneumonia was found at autopsy since this occurs with great frequency in moribund patients. As shown, 35 per cent of the 220 patients had active infectious disease at autopsy, and the incidence was not

TABLE VII
PRINCIPAL CAUSES OF DEATH AMONG 215 PATIENTS WITH POSTNECROTIC CIRRHOSIS

Group	Infection (%)	Gastro- intestinal Bleeding (%)	Liver Failure (%)	Heart Failure (%)	Miscel- laneous (%)	Not Determinable (%)
Total: 215 patients with postnecrotic cirrhosis	29	26	9	7	14	15
162 Patients with postnecrotic cirrhosis only 29 Patients with postnecrotic cirrhosis and	35	22	8	9	15	11
hepatic carcinoma	7	41	35	3.5	14	31
24 Patients with postnecrotic cirrhosis and fatty nutritional cirrhosis	17	33	29			21

lowered significantly (X2:1.95) in the years following the introduction and general use of antibiotics. The organ most frequently the site of infection was the lungs, usually involved by a bacterial pneumonia, followed by peritonitis and pyelonephritis. Among five patients with septicemia, a possible route of infection was suggested in two who had undergone laparotomy during the terminal admission, and one had infected decubitae. In the remaining two patients a mode of entry of bacteria was not apparent. Males outnumbered females among the patients with active infection at autopsy, 59 per cent males, a distribution corresponding to the predominance of males in this series. The ratio was reversed, however, in patients with active pyelonephritis, females outnumbering males (65 per cent females). The average age at death for the seventy-eight patients with infectious disease was fifty-seven years, corresponding to the average age of all patients in this study. The only group of patients with a significantly different average age was the group with active pyelonephritis, in which it was sixty-six

Among the 220 patients, tuberculosis was found in nineteen cases (9 per cent). This was an active infection in eight cases (4 per cent) and inactive in eleven cases (5 per cent). The approximate incidence of all forms of tuberculosis in autopsies at this institute is 9.4 per cent (18,218 autopsies), so that the incidence in patients with postnecrotic cirrhosis was comparable. Among patients with peritonitis, a possible source of infection was searched for; nine of the twenty-two patients had undergone surgery during the terminal admission, an additional three patients had had repeated paracenteses, and an additional five patients had

infections of intra-abdominal organs. These were perforated appendix, perforated duodenal ulcer, perforated fecalith of the sigmoid colon, perforated abscess of the Fallopian tube and a perforated gall bladder. In the remaining four patients, three had subdiaphragmatic abscess, pararenal abscess or chronic pyelonephritis. Thus in only one patient did the findings at autopsy fail to uncover the source of peritoneal infection. A surprising feature was that a diagnosis of intra-abdominal catastrophe was entertained clinically in only six (27 per cent) of the twenty-two patients with peritonitis.

Microorganisms in Infectious Diseases. Table 1x summarizes the microorganisms recovered from forty-five of the seventy-eight cases of infectious disease: in three additional cases there was no growth in bacterial cultures. Staphylococcus aureus and Escherichia coli were the most commonly recovered organisms, both before and during the years when antibiotics were in common use. Infection due to Streptococcus hemolyticus and Diplococcus pneumoniae almost entirely disappeared during the antibiotic years, with the exception of a single case of pneumococcal meningitis during the latter years. Clostridium welchii was recovered in a total of five cases, four of these in patients with peritonitis. In two cases it was the sole organism recovered; one of these was an instance of peritonitis, and the other a case of septicemia in which the organism was found in pure culture in the heart's blood, spleen, liver and lungs at autopsy. No evidence was found that patients with postnecrotic cirrhosis were especially prone to infection with gram-negative organisms [80].

Gastric and Duodenal Ulcers. Among 216 patients in whom the entire gastrointestinal tract was examined and described, 9 per cent of

TABLE VIII

ACTIVE INFECTIOUS DISEASE FOUND AT AUTOPSY AMONG 220 PATIENTS WITH POSTNECROTIC CIRRHOSIS

Infectious Disease	Total No.	No. Duplicated	No. (Excluding Duplicates)		
	110	Duplicated	Before 1945	1945–1956	
Pulmonary infection.  Active tuberculosis (8)  Lobar pneumonia (4)  Bronchopneumonia* (5)  Empyema (3)  Interstitial pneumonitis (2)  Septic infarction (1)  Pulmonary abscess (1)	24	0	9	15	
Peritonitis	22	4	8	10	
Renal disease.  Acute pyelonephritis (7) Chronic pyelonephritis (7) Acute glomerulonephritis (2) Chronic glomerulonephritis (2)	18	1	7	10	
Other infections.  Bacterial endocarditis (5) Septicemia (5) Meningitis (1) Prostatitis and cholangitis (1) Cellulitis (1) Skin pustules (1) Otitis media (1) Suppurative pancreatitis (1) Ischio-rectal abscess (1) Erysipelas and mastoiditis (1) Pulmonary granulomas, unknown etiology (1)	19	0	10	9	
Totals.	84	5	34	44	
Number excluding duplications		78	34	44	
Number with postnecrotic cirrhosis	220	220	81	139	
Per cent with infectious disease			42	. 32	

<sup>\*</sup> Excluding cases of slight or "terminal" bronchopneumonia found at autopsy.

patients had gastric or duodenal ulcers; the incidence of peptic ulcer in 18,486 autopsies at this institute was 5.5 per cent, a difference that was not of statistical significance (X<sup>2</sup>:3.82) since the figures for 18,486 autopsies did not exclude infant and stillborn autopsies. Among thirty-one patients with primary hepatic carcinoma in addition to postnecrotic cirrhosis, 16 per cent had ulcers, compared with 8 per cent of 185 patients with postnecrotic cirrhosis not complicated by primary hepatic carcinoma.

Of the twenty patients with ulcers, sixteen had gastric and four duodenal ulcers; ten of the twenty ulcers were either bleeding or had perforated. The incidence of gastric and duodenal ulcers would therefore appear to be greater in patients with primary hepatic tumor but the incidence in patients with uncomplicated postnecrotic cirrhosis is not significantly greater than in the general autopsy population.

Non-hepatic Neoplasms. Table x summarizes the neoplasms, other than those arising in the

TABLE IX

MICROORGANISMS RECOVERED FROM FORTY-FIVE OF A TOTAL OF SEVENTY-EIGHT CASES OF INFECTIOUS
DISEASE OCCURRING IN PATIENTS WITH POSTNECROTIC CIRRHOSIS

Microorganisms	Pulmonary Infection		Peritonitis		Septicemia, Meningitis, Endocarditis, Otitis Media		Totals
	Before 1945	1945–56	Before 1945	1945–56	Before 1945	1945–56	
Staphylococcus aureus	3 (2)*	2 (1)	1 (1)	3	1	3	13
Escherichia coli		1 (1)	3 (2)	5 (5)	1	1	12
Mycobacterium tuberculosis†	1	7	0	1	0	0	9
Diplococcus pneumoniae	5 (1)	0	1	0	0 .	1	7
Streptococcus hemolyticus	2 (1)	0	3 (1)	0	1	0	6
Clostridium welchii		0	2(1)	2 (2)	0	1	5
Proteus species	0	0	0	4 (4)	0	0	4
Aerobacter aerogenes		0	0	3 (3)	0	0	3
Streptococcus viridans		1	0	0	1	0	2
Streptococcus faecalis	0	0	0	2 (2)	0	0	2
Pseudomonas aeruginosa	0	1 (1)	0	0	0	0	1
Bacterium mucosus capsulatus	0	0	0	0	0	1	1
Hemophilus influenzae	0	1 (1)	0	0	0	0	1

\* Number in parentheses indicates cases in which one or more additional organisms were recovered.

† Establishment of infection as due to Mycobacterium tuberculosis was usually based upon morphological characteristics of the infective lesions.

liver, found among 221 patients with postnecrotic cirrhosis. Evidence that there is a decreased incidence of metastases to the cirrhotic liver [81] was not found in this series. Twenty-seven patients (27 per cent) had nonhepatic neoplasms and of these twelve had tumors showing some degree of invasion or metastasis. Of the twelve patients whose tumors showed invasion, six or 50 per cent had involvement of the liver. This is considered to be equal to or greater than the incidence of hepatic metastases in patients without cirrhosis at this institute.

Atherosclerosis and Myocardial Infarction. It has often been stated that patients with cirrhosis are less prone than the general populace to the development of atherosclerosis and myocardial infarction, although specific information concerning this relationship is difficult to obtain. Of the 221 patients in this study, a statement concerning atherosclerosis was made or a description of the aorta and blood vessels given in the autopsy protocols in 215 cases. Among these, 160 patients (73 per cent) were stated to have a moderate to severe degree of atherosclerosis, usually determined on the basis of placquing of the intima of the aorta, or of similar involvement

of major arteries. Only six patients had myocardial infarction; two of these were incidental, healed infarctions, and the other four were recent infarctions that resulted in death. The approximate incidence of myocardial infarction, both healed and acute, in autopsies at this institute during the years 1933 to 1956 (20,399)

TABLE X
NON-HEPATIC NEOPLASMS FOUND AT AUTOPSY AMONG 221
PATIENTS WITH POSTNECROTIC CIRRHOSIS

Neoplasm	No. of Patients	No. with Metastases	No. with Metastases to Liver
Carcinoma of pancreas	4	4	3
Carcinoma of esophagus	3	2	0
Gastrointestinal carcinoid	3	0	0
Carcinoma of prostate	2	1	0
Carcinoma of lung	2	1	0
Carcinoma of bowel	2 2 2 2	0	0
Carcinoma of uterus	2	2	. 1
Meningioma	2	0	0
Carcinoma of stomach	1	1	1
Carcinoma of kidney	1	1	1
Bronchial carcinoid	1	0	0
Papilloma of bladder	1	0	0
Carcinoma of tongue	1	0	0
Cystadenoma of ovary	1	0	0
Glioma of brainstem	1	0	0
Totals	27	12	6

autopsies) was approximately 10.3 per cent. No consistent control data are available for patients with atherosclerosis. It would appear that patients with postnecrotic cirrhosis have a lower incidence of myocardial infarction than the general autopsy population, but statements concerning a comparison of atherosclerosis cannot be made.

Rheumatic Heart Disease. Rheumatic heart disease was found at autopsy in eleven of 221 patients in this study (5 per cent). The incidence of rheumatic heart disease in all autopsy cases at this institute (approximately 18,000 autopsies) is 3.9 per cent, a comparable figure.

#### CASE REPORTS

Two cases with hepatic carcinoma complicating postnecrotic cirrhosis are presented.

CASE I. This sixty-six year old single unemployed white man entered the Boston City Hospital for the second time, twenty-four days prior to death, complaining of epigastric pain of eight weeks' duration. He had been in relatively good health until the onset of a dull, constant, generalized abdominal ache, with superimposed episodes of sharp epigastric pain. At about the same time he had noted a dark colored urine on several occasions, but he had not noticed jaundice. The patient had been addicted to the use of morphine for approximately thirty years but denied use of the drug during the past eight years. Six years before the present admission he had been hospitalized with painless jaundice lasting two weeks. At that time he had had a negative blood Hinton test, serum total protein of 7.1 gm. per cent, prothrombin time 100 per cent of normal, a 3-plus formol gel test, and persistent 1-plus bile in his urine. The diagnosis made at that time was viral hepatitis. The patient gave no history of other serious illnesses. His nutritional intake had usually been poor because of excessive use of alcohol.

On physical examination he was a thin icteric white man complaining of abdominal pain and tenderness in the right upper quadrant. His blood pressure was 120/80 mm. Hg and his temperature was 98.6°F. orally, with daily rises to 100°F. The liver edge was barely palpable and tender; the spleen could not be felt; there was slight prominence of the abdomen, with shifting dullness. Laboratory tests showed a hematocrit of 37 per cent, hemoglobin of 12.5 gm. per cent, a white blood cell count of 5,850 cells per cu. mm., with a differential count of 64 per cent polymorphonuclear leukocytes, 33 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The urine sediment contained 3 to 4 white blood cells per high power field. There was 1-plus bile and protein. The blood non-protein nitrogen was 35 mg. per cent, the fasting blood sugar was 70 mg. per cent. The stool

gave a 2-plus guaiac reaction. The total serum protein was 6.6 gm. per cent, prothrombin times were 37 and 32 per cent of normal. The cephalin flocculation test was 3-plus positive. The serum alkaline phosphatase was 8.4 Bodansky units and the icteric index was 35 units.

The patient was treated with bed rest, a regular diet, and opiates were given for pain. A gastrointestinal x-ray series was negative despite the guaiacpositive stools. The abdominal pain increased in severity, requiring larger doses of opiates; edema appeared, ascites increased, and the patient became extremely weak and finally moribund. He died quietly on his twenty-fourth hospital day. The final clinical diagnosis was carcinoma of the head of the pancreas. At autopsy a postnecrotic type of cirrhosis was found, with a primary hepatic cell carcinoma that had metastasized to the lungs, and was growing within the portal vein. An acute pancreatitis was also present. There was 300 ml. of bloody ascitic fluid; the liver weighed 1,880 gm., and was composed of multiple yellow-gray nodules of varying sizes, the majority 2 to 6 cm. in diameter, with soft yellow masses of tumor tissue throughout the liver. The spleen weighed 450 gm. There was marked atherosclerotic calcification of the large arteries, especially the abdominal aorta. No esophageal varices or peptic ulcers were found. Microscopically the liver away from tumor showed dense fibrous bands separating irregular nodules of liver tissue.

CASE II. This thirty-six year old white married male electrician was admitted to the Boston City Hospital for the second time, seventeen days before death, in a state of coma. He had begun to eat breakfast in bed at home when he lapsed into an unresponsive state from which he could not be aroused. His previous admission to this hospital had been four months earlier for what had been diagnosed as inoperable, metastatic carcinoma, probably originating in the islet cells of the pancreas. During his earlier admission he had had persistent epigastric pain and an enlarged liver. A biopsy specimen of the liver had been reported to show metastatic carcinoma, possibly of islet cell origin. Liver function tests at that time had shown a bromsulphalein retention of 40 to 56 per cent, a total serum protein of 6.7 gm. per cent with albumin of 3.1 and globulin of 3.6 gm. per cent. Alkaline phosphatase values had been 25, 69 and 31 Bodansky units. Formol gel and cephalin flocculation tests had been negative; prothrombin times had been 100 per cent of normal. Icterus had been present, with icteric indices of 25 and 40 units, and the stools had been negative for occult blood on five occasions. The urine had contained 1-plus bile and urine urobilinogen in a dilution of one to four. During the interval between hospital admissions he had had frequent episodes of weakness and lethargy, but no relationship to intake of food had been observed. The

past history was of interest in that ten years before death, while the patient was in the merchant marine, he had spent three and a half months in a marine hospital with "indigestion." Diagnostic studies had not revealed a cause for this and, in large part because of the lack of physical and laboratory findings, the diagnosis upon discharge had been "neurasthenia" and "indigestion." The patient denied use of alcohol in any quantity both at the present and at all times in the past. His nutrition was said to be good except for the year prior to death when his appetite had been poor, but he nevertheless preferred a diet of "pork kidneys and vegetables." His only other previous illnesses or hospital admissions had been at the age of ten, when he had undergone an uncomplicated tonsillectomy. There was no history of syphilis, parenteral injections or blood transfusions. He had been married for two years and had one child.

On physical examination the patient was in deep coma and was perspiring freely. Glucose was administered intravenously and a dramatic response was observed as the patient regained consciousness. Vital signs included blood pressures of 130/60 and 130/70 mm. Hg; throughout his hospitalization his temperature ranged daily from 98° to 99°F. orally. The liver was palpable 15 cm. below the costal margin and nodular; the spleen was not palpable. There was shifting abdominal dullness consistent with ascites, but it did not require paracentesis. Jaundice was present, and the stools gave persistent 1- to 4-plus guaiac reactions.

The hematocrit on admission was 31 per cent but steadily dropped to 24 per cent, and blood transfusions were given. During hospitalization these totalled eleven. The white blood cell count was 14,000 cells per cu. mm. with 51 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes and 4 per cent monocytes. The urine sediment contained 3 to 5 white blood cells and rare red blood cells per high power field. Four-plus bile was noted on all occasions with 1- to 2-plus protein, and urobilinogen in dilutions of one to four. The bromsulphalein retention was 40 per cent, the total serum protein 5.7 gm. per cent with 3.4 gm. per cent albumin and 2.3 gm. per cent globulin. The prothrombin times were 47, 37, 32 and 30 per cent of normal. Formol gel and cephalin flocculation tests were negative. The serum alkaline phosphatase values were 11.2, 25.6 and 31.5 Bodansky units. The icteric index was 46 units, rising to 70 units. The blood urea nitrogen was 8 mg. per cent. Fasting blood sugar values were in the range of 36 to 43 mg. per cent during periods of coma, and never rose above 86 mg. per cent without intravenous glucose therapy.

The patient was given a high protein, low fat diet, blood transfusions, vitamin K and glucose was administered intravenously. Throughout his admission he had recurring episodes of stupor with dramatic responses to intravenously administered glucose. He continued to have persistently guaiac-positive, at

times frankly bloody stools; he died with hypotension on his seventeenth hospital day. The final clinical impression was islet cell carcinoma with metastases and gastrointestinal bleeding of undetermined site.

At autopsy postnecrotic cirrhosis and primary hepatic cell carcinoma (hepatoma) were found, with metastases to regional lymph nodes and to both lungs. A large chronic duodenal ulcer was present, with abundant blood in the gastrointestinal tract. Esophageal varices were not demonstrated. The liver weighed 6,100 gm., was green, with large irregular nodules, many yellow in color representing areas of tumor. Approximately three-fourths of the liver was replaced by tumor. There was 1,500 ml. of ascitic fluid; the spleen weighed 415 gm. Microscopically the liver in areas removed from the tumor showed broad fibrous bands separating nodules of regenerating liver tissue. The tumor was a characteristic hepatoma.

An example of postnecrotic cirrhosis complicated by fatty nutritional cirrhosis is summarized:

CASE III. This thirty-nine year old white unemployed man was admitted to the Boston City Hospital for the sixth time, three days before death, with complaints of abdominal swelling and increasing lethargy. He had left this hospital against medical advice only two days earlier, at which time he was being treated for cirrhosis and hepatic decompensation.

At the age of eleven the patient had had an illness characterized by jaundice, and since that time he claimed to have frequently noted a yellow color to his sclerae. Further details of the initial illness were not given. He first became known to this hospital only four months before death, at which time he was treated for cirrhosis and chronic alcoholism. His health since his childhood illness had been good, but the patient had not worked, and he had consumed beer and whiskey daily since about the age of nineteen years. During his first admission his liver and spleen were not palpable. Ascites was noted. The blood pressure was 145/80 mm. Hg. His hematocrit was 36 per cent, the white blood cell count was 11,500 cells per cu. mm. with 69 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 2 per cent monocytes. His blood Hinton test was negative. The stools were negative for occult blood. The patient was jaundiced, with an icteric index of 60 units, and there was 4-plus bile in the urine, with no protein and a negative sediment. The blood urea nitrogen was 8 mg. per cent, the fasting blood sugar 97 mg. per cent. The cephalin flocculation test was 4-plus positive. The patient left the hospital against medical advice, but he was readmitted in one month with anasarca, having continued to drink beer and whiskey to excess. Abdominal paracentesis was performed and 13,000 ml. of clear fluid was removed. During the following three months until death the patient was readmitted on three

occasions, each time with ascites, edema and jaundice. The liver and spleen were not palpable on any admission. The formol gel and cephalin flocculation tests were persistently abnormal. The total protein was 7.0 gm. per cent, with albumin of 1.7 gm. per cent and globulin 5.1 gm. per cent.

The patient had had two admissions to other hospitals. At the age of eight he had had a tonsillectomy, and at the age of twenty-four he had had an appendectomy. His only other serious illness had been

pneumonia five years before death.

On admission the patient was a jaundiced, poorly nourished white man in a state of stupor. His blood pressure was 84/44 mm. Hg and his temperature ranged between 98.8° and 96°F. orally during hospitalization. His liver and spleen were not palpable. The hematocrit was 34 per cent, the white blood cell count was 12,700 cells per cu. mm. with 79 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. The icteric index was 70 units, and the blood non-protein nitrogen 136 mg. per cent. The stools were negative for occult blood. The patient was given a salt-free diet and vitamins. His stupor progressed to coma and he died on his third hospital day. The final clinical diagnosis was Laennec's cirrhosis and hepatic coma.

At autopsy postnecrotic cirrhosis was found in addition to fatty infiltration of the liver and a portal cirrhosis. There was 6,000 ml. of clear ascitic fluid present, with fluid in both thoracic cavities. Atelectasis of the left lung was present. On neuropathological examination there was an incidental meningioma without invasion or distant spread. The liver weighed 1,350 gm. and was described as "hobnailed" and "nodular," the nodules averaging 2 to 3 cm. in diameter, and of a gray-brown color. In addition, intervening areas of liver were light brown and finely nodular, the nodules approximately 0.2 to 0.6 cm. in diameter. The spleen weighed 400 gm. Microscopically the liver was composed of nodules of liver tissue separated by broad fibrous bands. In addition, thin fibrous strands bridged adjoining portal areas, and many liver cells contained fat. "Alcoholic hyaline" or "Mallory bodies" were found in many liver cells.

The following case represents a patient with an episode of jaundice followed by onset of abdominal pain and death in approximately three years.

CASE IV. This fifty-nine year old white male plumber entered the Boston City Hospital for the second time eight months before death, complaining of crampy low abdominal pain of several months' duration. Two years before this admission he had been treated for syphilis on the basis of a positive serological test, and he had received approximately 30 bismuth and arsphenamine injections. These had been dis-

continued because after approximately three months of treatment he had experienced epigastric distress, and his liver became palpable although no jaundice had been observed.

His first admission to this hospital had been one and a half years before death for an acute alcoholic state. At that time the serological test for syphilis had still been positive. His liver had been felt 10 cm. below the costal margin. The hemoglobin at that time had been 15 gm. per cent, total serum protein 6.3 gm. per cent with albumin of 3.3 gm. per cent and globulin of 3.0 gm. per cent. The cephalin flocculation test had been 3-plus positive, and there had been 24 per cent bromsulphalein retention.

The patient had been a user of alcohol for approximately thirty years, stating that he usually took "2 whiskeys and 12 ales" per day. His nutrition had been generally good except when drinking to excess, at which times he ate little but an occasional sandwich. During the influenza epidemic of 1918 he had contracted that disease, at the approximate age of twentynine years. At about the same age he had undergone an uneventful hernia repair. Four years before the present admission he had all his teeth removed by a dentist.

On physical examination he was a thin, alert, cooperative white man without icterus, with a blood pressure of 190/105 mm. Hg, and normal temperature. His liver and spleen were not palpable; there was no demonstrable ascites. The hematocrit was 2.7 per cent; the hemoglobin 8 gm. per cent; the red blood cell count 4.3 million per cu. mm. The white blood cell count was 3,900 cells per cu. mm. The urine contained no bile, and the sediment had only an occasional red blood cell per high power field. The stools were negative for occult blood; the blood non-protein nitrogen was 45 mg. per cent; the prothrombin time was 100 per cent of normal. The cephalin flocculation test was negative. The total serum protein was 6.0 gm. per cent.

The patient was treated with a high protein diet and antibiotics. Because of persistent low abdominal pain and a gastrointestinal x-ray series that showed filling defects of the stomach, exploratory laparotomy was performed. Gastric and large bowel polyps were found which were benign on pathological examination. Complications of abscess formation in the lower abdomen and atonic bowel developed, necessitating further surgery. After a protracted hospital stay and several operations, the patient failed in strength and died what was termed a "respiratory death," with cyanosis and dyspnea. The final clinical diagnoses were cirrhosis and pneumonia.

At autopsy postnecrotic cirrhosis was found, and a previously unsuspected bronchogenic carcinoma of the right upper lobe of the lung, with abscess formation and metastases to hilar lymph nodes. A localized peritonitis and abscess in the right lower quadrant were also present. The liver weighed 1,670 gm., and

was composed of yellow and brown nodules averaging 0.7 to 1.0 cm. in diameter, with occasional larger nodules approximately 1.5 to 2.0 cm. in diameter. Intact esophageal varices were found; there was no ascites; the spleen weighed 300 gm. The gall bladder contained multiple soft black stones averaging less than 0.5 cm. in diameter; there was no acute inflammation or ductal obstruction. The coronary arteries were narrowed by atherosclerosis, and the aorta contained yellow placques, especially in the abdominal portion. Microscopically the liver was composed of irregular nodules of liver cells, separated by broad fibrous bands which contained plasma cells and mononuclear cells, and abundant bile duct proliferation.

The following case represents a patient with a long asymptomatic interval following an episode of jaundice, death occurring in a relatively short period of time after recurrence of jaundice.

Case v. This fifty-three year old male railway fireman was admitted to the Boston City Hospital for the first time eighteen days before death because of abdominal swelling and jaundice of two weeks' duration. At the age of eighteen years he had had a severe illness with jaundice lasting several weeks. Upon recovery he had been relatively well, however, and able to carry on physical labor. He had been a moderate user of beer and whiskey since the age of twenty-two years, but he had always been regularly employed; his diet was said to be good. He gave no history of other illnesses, and there was no mention of previous syphilis.

On physical examination the patient was a poorly nourished, icteric white man with a palpable and tender liver 6 cm. beneath the right costal margin, ascites and a palpable spleen. His blood pressure was 140/80 mm. Hg, and his temperature ranged between 97.6° and 98.6° F. orally. Cervical and axillary lymph nodes were noted to be palpable. His hemoglobin was 80 per cent of normal, the red blood cell count was 4.1 million per cu. mm. and the white blood cell count was 11,500 cells per cu. mm. The urine contained 3-plus bile on several occasions, with a trace of protein, and the sediment was negative. The icteric index was 30 units, rising to 60 units; the blood nonprotein nitrogen was 32 mg. per cent. Liver function tests were not performed. The stools gave a 4-plus guaiac reaction on several occasions. The patient was treated with sedatives and demerol® for restlessness and abdominal pain. A cervical lymph node biopsy showed metastatic carcinoma, probably originating in the stomach. The patient vomited blood on several occasions in the hospital, beginning ten days before death, and totalling an estimated liter; he lapsed into coma and died on his eighteenth hospital day. The final clinical diagnosis was carcinoma of the stomach with gastrointestinal bleeding.

At autopsy postnecrotic cirrhosis and carcinoma of the stomach, metastatic to the liver, regional lymph nodes and the adrenals were found. The bleeding site was found to be the gastric neoplasm. There was also fibrocaseous tuberculosis of the right upper lobe of the lung, and bronchopneumonia. The liver weighed 2,460 gm., and was green, nodular, and contained metastases from the gastric tumor. There were 500 ml. of clear ascitic fluid, 3,600 ml. having been removed shortly before death. The spleen weighed 200 gm.; the coronary arteries contained atheromas, and the abdominal aorta had many calcific intimal placques. Esophageal varices were found which were intact. Microscopically the liver contained metastatic tumor, in addition to postnecrotic cirrhosis.

The following two cases represent patients with a long asymptomatic period following an episode of jaundice, and relatively long survival after recurrence of jaundice or occurrence of abdominal pain or ascites.

Case vi. This seventy-six year old white man was admitted to the Boston City Hospital for the second time nine days before death, because of abdominal swelling of four months' duration. His first admission to this hospital had been three months prior to death, at which time he also complained of ascites and had had a paracentesis. He had been discharged as unimproved two months before death. The patient had formerly been a printer; his only serious illness had been syphilis at the age of forty-eight, for which he had received a course of injections of arsenicals and bismuth, beginning when he was fifty-nine years of age. After receiving injections for approximately one year jaundice developed and treatment was discontinued. He was in good health until the age of seventy-three, approximately three years before death, when he had again had two brief episodes of jaundice. Since that time he had considered himself to be in poor health. He denied use of alcohol at all times during his life; his diet had generally been good until three years before death, when he ate poorly and generally avoided meat in his diet, preferring vegetables. Ascites had occurred for the first time approximately four months before death.

On physical examination the patient was a well nourished, elderly white man in no acute distress. His blood pressure was 170/90 mm. Hg on admission; temperatures ranged between 98.6° and 99°F. orally; there was no icterus. His abdomen was protuberant, and after 6 L. of clear ascitic fluid were removed, the liver was palpable 2 cm. below the costal margin but the spleen could not be felt. The hematocrit on admission was 39 per cent, the hemoglobin was 13 gm. per cent, and the white blood cell count was 4,100 per cu. mm. with 49 per cent polymorphonuclear leukocytes and 51 per cent lymphocytes. The blood Hinton test was positive. The urine contained no bile; there

was 3-plus albumin; the sediment contained 2 to 5 red blood cells per high power field on two occasions. The blood non-protein nitrogen was 25 and 32 mg. per cent; the total serum protein was 5.1 gm. per cent, the prothrombin time 38 per cent of normal, the cephalin flocculation test was 4-plus positive. The serum alkaline phosphatase was 3.8 Bodansky units. Urine urobilinogen was positive in a dilution of 1 to 16. The stools were negative for occult blood on admission.

The patient was treated with digitalis and a saltfree diet, vitamins and two paracenteses. On the seventh hospital day he vomited dark brown blood and became stuporous. The stools became 3-plus positive for blood, and the urine contained many red blood cells. He died in coma on his ninth hospital day. The final clinical diagnoses were cirrhosis of unknown type, and syphilis, probably involving the central nervous system. At autopsy postnecrotic cirrhosis, 4 L. of clear ascitic fluid, bronchopneumonia, and intact esophageal varices were found. The gastrointestinal tract contained only small amounts of old blood, without a definite bleeding site. The liver weighed 950 gm., and was coarsely nodular, the majority of nodules being greater than 1 cm. in diameter; it was of a diffusely grey color, firm and fibrous. The spleen weighed 280 gm. The heart weighed 250 gm., with moderate atherosclerotic narrowing of the coronary arteries and extensive placquing of the intima of the abdominal aorta. Microscopically, nodules of liver tissue with uninvolved portal areas were separated by broad fibrous bands in which there were lymphocytes, macrophages and many small bile ducts.

CASE VII. This thirty year old single Albanian man entered the Boston City Hospital three days before death because of vomiting of blood the previous day, and onset of semi-coma the day of admission. The patient had had hepatitis in Albania during the second World War, approximately fifteen years earlier; at that time he had been subsisting on an inadequate diet. Following the initial illness he had felt well, and had emigrated to the United States approximately six years before admission. Four years before admission he had been admitted to another hospital because of hematemesis. A splenorenal shunting operation had been performed. A liver biopsy had shown postnecrotic cirrhosis. He had been in relatively poor health since undergoing surgery, with occasional brief episodes of painless jaundice. During an admission two years before death the serum alkaline phosphatase had been 18 Bodansky units in the presence of moderate jaundice; the cephalin flocculation test had been 2-plus positive, and the serum globulin had been 6.4 gm. per cent. The patient did not use alcohol in any amount, and since living in this country he had apparently had an adequate diet. He had been employed as a waiter and as a clerk.

On physical examination he was a well nourished, icteric white man in semi-coma. The liver was felt 4 cm. below the costal margin and it was very hard; the spleen was absent. Blood pressure was 146/80 mm. Hg; temperature was 103.2°F. orally, rising terminally to 106.6°F. The hematocrit was 21 per cent on admission, rising to 30 per cent after 1,000 ml. of blood was given. The white blood cell count was 13,500 cells per cu. mm. with 60 per cent polymorphonuclear leukocytes, 39 per cent lymphocytes, and 1 per cent monocytes. The urine contained 2-plus bile, no protein, and 2 to 3 red blood cells and 4 to 6 white blood cells per high power field. The blood non-protein nitrogen was 45 mg. per cent, the serum bilirubin 6.7 mg. per cent, the total serum protein 6.0 gm. per cent, the cephalin flocculation and formol gel tests were both 4-plus positive, and the arterial blood ammonia was 406 µg. per cent. The stool was 4-plus positive for occult blood. The patient was treated with transfusions, antibiotics and vitamins. He became agitated and delirious, then lapsed into deep coma and died on his third hospital day. The final clinical diagnoses were postnecrotic cirrhosis following viral hepatitis, hepatic coma and gastrointestinal bleeding, probably from esophageal varices. At autopsy postnecrotic cirrhosis, acute cholangitis and pericholangitis, and bronchopneumonia were found. The splenorenal anastomosis was intact and functioning. Two small accessory spleens were present. The liver weighed 4,500 gm. and was grey and green, with irregular nodules ranging from 0.8 to 2.0 cm. in diameter. The ileum and large bowel contained small amounts of black semiliquid material consistent with altered blood. No bleeding point was found, however, and esophageal varices could not be demonstrated despite a careful examination. Microscopically the liver was composed of varying sized nodules of liver tissue separated by broad fibrous bands containing lymphocytes, plasma cells and many small bile ducts.

#### COMMENTS

Because of differences in criteria and terminology, an extensive comparison has not been made between the findings in the present series of cases and earlier reports of postnecrotic cirrhosis. Such a comparison would be confused by the fact that in most studies of postnecrotic cirrhosis, the number of cases from which conclusions have been drawn has been small, the series have been highly selected, and the diagnoses have been often based in part on clinical and laboratory features as well as upon morphologic findings. In this laboratory a differentiation of various types of cirrhosis is based almost wholly on morphologic criteria [4]; these criteria, as set forth in detail by Mallory [1,9,82],

have been more or less constant for five decades. This system has been used in the present study because it offers a degree of consistency, although it is recognized that morphologic classifications are open to criticisms, one of which is that different etiologic types of liver damage may ultimately result in the same morphologic picture. The recent increases in postnecrotic cirrhosis in autopsies at this hospital [4,5], with concomitant increases in hepatic carcinoma, are not explained in the present study. It is possible that the present large number of cases of postnecrotic cirrhosis reflects a high incidence of previous viral hepatitis transmitted during antisyphilitic and other parenteral therapy, but this cannot be proved from present data. If the high incidence of postnecrotic cirrhosis does reflect previous hepatitis, then the hepatitis must often have been of non-icteric form. Although data to support the concept that cirrhosis follows hepatitis is considered to exist in the present study, the evidence is largely inferential.

The clinical course of patients with previous jaundice (presumably representing a viral hepatitis) is of interest in considering the two divergent paths that may be taken. If these are the courses taken by patients with hepatitis in whom postnecrotic cirrhosis develops, then three factors make difficult any attempts to follow-up patients with hepatitis during life in order to observe the development of cirrhosis. The first is what must be the rare occurrence of cirrhosis after hepatitis, since although viral hepatitis is relatively common, a diagnosis of postnecrotic cirrhosis is not frequently made. However, the number of patients with viral hepatitis who recover without residual hepatic damage may be less than previously supposed. The second feature rendering clinical studies difficult is that many of the patients in the present study gave no past history of jaundice, so that if they had viral hepatitis in the past, it must have been of a non-icteric form. This presents the difficult problem of detecting non-icteric hepatitis. The third feature is the long interval, in many cases, between an episode of hepatitis and the development of cirrhosis. A large number of symptomfree persons with apparent recovery from hepatitis would have to be followed-up for as long as fifteen years to detect only a few in whom cirrhosis might develop. It is possible that before these handicaps to clinical study are overcome, viral hepatitis will have been readily produced in the laboratory animal, and the role of hepatitis

in causing cirrhosis will have been elucidated in this way.

No evidence was found in past clinical histories of patients in this study that postnecrotic cirrhosis occurred in patients who had previously had a severe, near-fatal hepatic injury. The concept that such is the case has been based partly on Bergstrand's observations [83] and partly upon speculation. It would appear that until better supporting evidence is available, this concept should be questioned. The role of complicating factors such as alcoholism, poor nutrition and severe intercurrent illness occurring in patients with hepatitis also was not confirmed in the present study, inasmuch as these features bore no constant relationship to the occurrence of cirrhosis.

It is somewhat surprising that the patients in this study did not have elevated serum globulins, as has been reported in many studies of postnecrotic cirrhosis. Again, differences in criteria for diagnosis, considerable selection of cases, and the small number of cases from which conclusions have been drawn in the past are among factors that make comparison difficult. For example, many of the cases termed postnecrotic cirrhosis by Scandinavian workers would probably be considered to represent subacute atrophy of the liver if examined in this laboratory and, as stated earlier, cases of acute and subacute hepatic atrophy were not included in the present study.

It is of interest that of forty-nine patients in this study who died with bleeding from esophageal varices, death in forty-four occurred during the first admission for hematemesis or melena, and only five patients of 100 with varices had survived a previous episode of bleeding without undergoing surgery. This may be relevant in considering the so-called "prophylactic" surgical procedure for eophageal varices, in which a shunting procedure is undertaken as soon as varices are discovered, before even a first episode of hematemesis occurs. From the present limited observations such an approach would appear to be warranted on a tentative basis in patients with postnecrotic cirrhosis, since the mortality from bleeding varices is extremely high with the first bleeding episode.

A noteworthy feature is the frequency with which primary hepatic carcinoma occurs in postnecrotic cirrhosis (14 per cent of cases in the present series). One factor of possible importance is the marked regenerative activity that takes

place in the hepatic cells in postnecrotic cirrhosis, and which appears to be greater than the regenerative activity that is usually observed in other types of cirrhosis. Further study of this phenome-

non would appear to be warranted.

Finally, although statements have been made in the past that postnecrotic cirrhosis does not represent a true cirrhosis, and terms such as postnecrotic scarring rather than cirrhosis have been applied to the condition, there is little doubt from the present study that the morphologic entity of postnecrotic cirrhosis has clinical features that are only slightly, if at all, different from most other types of cirrhosis.

#### SUMMARY AND CONCLUSIONS

1. An analysis is presented of the clinical, laboratory and pathological features of 221 cases of postnecrotic cirrhosis in which autopsies were performed at the Mallory Institute of Pathology

during the years 1917 to 1956.

- 2. Limited and inferential evidence is presented that cirrhosis of the postnecrotic type may follow hepatitis. No evidence was found, however, that a sudden and massive liver insult had occurred in such patients. Twenty-four per cent of patients in this study had had a previous episode of jaundice, and an additional 44 per cent had been exposed to greater than usual risk from serum hepatitis in the course of receiving antisyphilitic and other parenteral injections. As a control group, sixty-one patients with hemochromatosis and pigment cirrhosis were studied and, in this group, the incidence of jaundice was 3 per cent, of syphilis 9 per cent and of surgical procedures 34 per cent.
- 3. Patients with postnecrotic cirrhosis at autopsy who had a history of previous jaundice (presumably viral hepatitis) had followed one of two clinical courses after the episode of jaundice. Two-thirds of patients had been relatively well for a period of years (average of fifteen years), after which time ascites, jaundice or right upper quadrant pain had occurred. From the time of appearance of these features the duration of life was only two months in two-thirds of the group, but it averaged six years for the remaining onethird of the group. The second clinical course was followed by approximately one-third of patients. In this group the interval from jaundice to the occurrence of ascites, recurring jaundice or right upper quadrant pain was less than a year, and the length of survival once these signs appeared averaged only seventeen months.

4. The average duration of continuous illness before hospitalization was less than six months in more than one-half of the patients in this study. Only about one-fifth of the patients had been continuously ill for more than two years. After admission to the hospital, the average duration of life was twenty-two days.

5. The presenting complaints of patients in this study were chiefly ascites and edema (30 per cent), abdominal pain (17 per cent) and hematemesis (14 per cent). Abdominal pain was especially frequent among patients with hepatic

carcinoma.

6. Such features as age and sex of the patients in this study did not differ greatly from other patients with cirrhosis or from the general autopsy population of this institute. A racial difference was noted in that postnecrotic cirrhosis was relatively frequent among Chinese, although the number of Chinese patients was small.

7. Approximately one-half of the patients in this series had consumed alcoholic beverages to excess; the other half drank little or no alcohol. An adequate diet was claimed by approximately two-thirds of patients. Poor nutrition and alcoholism were common in patients who had fatty nutritional (alcoholic) cirrhosis in addition to postnecrotic cirrhosis.

8. Laboratory and liver function tests were characteristic of patients with cirrhosis but no specific alterations for postnecrotic cirrhosis were

found.

9. At autopsy, the liver tended to be smaller than normal; 76 per cent of livers weighed less than 1,500 gm.; the color of the liver was most often gray to yellow, and nodules of liver tissue tended to be large and irregular, generally greater than 2 cm. in diameter, and separated by broad fibrous scars; but the occurrence of large hepatic nodules was not an invariable finding.

10. The spleen tended to be enlarged at autopsy, with average weights between 350 and 400 gm. A palpable spleen was not of help in determining the presence or absence of hepatic

carcinoma or of esophageal varices.

11. Bloody ascites was found in 23 per cent of patients with hepatic carcinoma compared with a frequency of only 2.5 per cent of patients with uncomplicated postnecrotic cirrhosis.

12. Esophageal varices were found at autopsy in 52 per cent of patients; of these, one-half showed evidence of active, recent bleeding. Of forty-nine patients who died with bleeding from

varices, forty-four died during their first hospital admission for bleeding.

13. The principal causes of death among patients in this study were infection (29 per cent) and gastrointestinal bleeding (26 per cent), the latter usually from esophageal varices. A slight or "terminal" bronchopneumonia was not included among cases with infection.

14. A total of 35 per cent of patients had infectious disease at autopsy, and these were chiefly pneumonia, peritonitis and pyelonephritis. Gram-negative organisms were not especially prevalent as etiologic agents. The frequency of infection in the years following the introduction of antibiotic therapy was not significantly lower (32 per cent) than in the years before the introduction of antibiotic therapy (42 per cent).

15. Gastric and duodenal ulcers were found in 9 per cent of patients with postnecrotic cirrhosis, compared with an incidence of 5.5 per cent in all autopsies at this institute, a difference that is not statistically significant. However, 16 per cent of patients with concurrent hepatic carcinoma had peptic ulcer.

16. Non-hepatic neoplasms were found in 12 per cent of patients; metastases to the liver in patients with postnecrostic cirrhosis appeared to be of the same order of frequency as in patients without cirrhosis.

17. Attention is called to the frequency with which primary hepatic carcinoma occurs in postnecrotic cirrhosis (14 per cent of cases). Relatively few diagnostic features clinically distinguish patients with postnecrotic cirrhosis and hepatic carcinoma from patients with uncomplicated postnecrotic cirrhosis. In this series, features of only limited value because of their late occurrence included abdominal pain (chiefly in the right upper quadrant), bloody ascites, marked cachexia, and a slightly elevated serum alkaline phosphatase.

18. Some controversy has existed in the past as to whether or not the morphologic picture of postnecrotic cirrhosis represents a clinical disease. From the present study there is little doubt that postnecrotic cirrhosis is both clinically and anatomically a true cirrhosis.

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# Circulatory Changes in Chronic Liver Disease\*

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HYPERKINETIC circulatory state may be associated with chronic disease of the liver [1]. Evidence of increased peripheral flow is shown by warm, flushed extremities, bounding pulses and capillary pulsations, and an increased cardiac output by tachycardia, an active precordial impulse and frequently an ejection systolic murmur. There are few laboratory observations in support of these clinical features. Kowalski and Abelmann noted an elevated resting cardiac index in approximately one-third of patients with Laennec's cirrhosis and chronic alcoholism; these patients also had a low peripheral vascular resistance and a calculated decrease in arteriovenous oxygen difference [2]. An increased peripheral flow was demonstrated in a small number of patients with liver disease [3] and confirmed in a larger series of cirrhotic patients by Martini and Hageman [4].

Another abnormal circulatory finding in chronic liver disease is arterial unsaturation, possibly due to a shift in the oxygen dissociation curve [5] or to shunting of systemic venous blood through pulmonary arteriovenous anastomoses [6]. Also, an increased plasma volume or total blood volume has been reported and correlated with the portal-systemic collateral circulation [7,8], arterial desaturation [8] and a "hypervolemic" anemia (9).

The following report describes the circulatory changes in twenty-four patients with chronic portal cirrhosis and six patients with chronic biliary cirrhosis. In addition, six patients with extrahepatic portal vein obstruction were investigated to determine the circulatory effects of a portal-systemic circulation with a normally functioning liver. These three groups were compared with fourteen control subjects.

MATERIALS AND METHODS

Selection of Patients. All twenty-four patients with portal cirrhosis had histological proof of the diagnosis. The disease followed infectious hepatitis in five cases and was associated with chronic alcoholism in three subjects. One subject had hemochromatosis, one patient had Wilson's disease. No definite etiology could be found in fourteen patients. Seven patients had had a surgical portacaval anastomosis at least six months prior to study.

There were four cases of primary biliary cirrhosis, one patient with common duct stricture and one patient with chlorpromazine jaundice of eighteen months' duration. These patients were all icteric.

Six patients with extra-hepatic portal vein obstruction had surgical or portal venographic [10] evidence of portal vein obstruction with an extensive collateral circulation, normal liver function and a histologically normal liver. One patient had had a portacaval anastomosis.

Twenty-seven of the thirty-six patients studied had venographic, surgical or autopsy estimation of the presence and magnitude of a portal-systemic venous collateral circulation. In nine patients, assessment was made on clinical grounds and by radiological examination of the esophagus. The portal-systemic collateral circulation was graded zero (absent), one plus (moderate) or two plus (extensive).

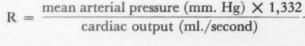
The fourteen control subjects were ward patients or laboratory staff.

Procedures. All studies were made on resting, fasting subjects. Cardiac output was determined by the dye dilution method and calculated from the Hamilton formula [11]. The technic used to

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measure cardiac output with Evans blue dye and an ear oximeter has been reported in detail from this laboratory [12]. In twelve patients dye was injected into the right atrium or pulmonary artery at the time of cardiac or hepatic vein catheterization; all other patients had intra-



Arterial oxygen saturation was determined by a modified Haldane [16] method and the per cent saturation calculated.

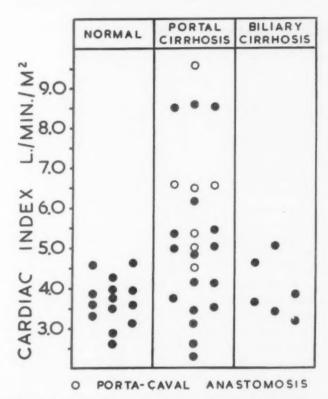
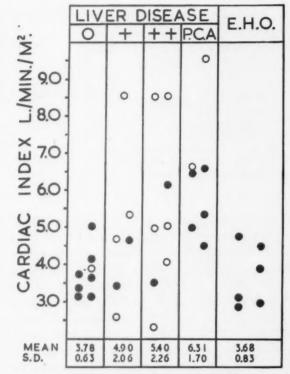


Fig. 1. The range of cardiac indices in normal adult subjects and in patients with portal cirrhosis and biliary cirrhosis. Normal =  $3.68 \pm 0.6$  L./minute/Sq. M. Hollow circles represent patients with portacaval anastomosis.

venous injections. Surface area estimation used in calculating cardiac index was obtained from the Du Bois formula using the patient's height and weight when free of ascites and edema.

Plasma volume was determined from the Evans blue dye concentration obtained by a modified extraction method [13] in a blood sample drawn ten minutes after the dye injection [14]. Peripheral venous or arterial hematocrits used in the calculation of total blood volume and cardiac output were corrected for trapped plasma and total body hematocrit as described by Mollison [15].

Phasic arterial pressure was measured with an indwelling arterial needle and a Statham strain gauge (P-23A); the mean pressure was determined by planimetry. Peripheral vascular resistance was determined by the formula:



SERUM ALBUMIN >3.0 GMS. %
 SERUM ALBUMIN 3.0 GMS. % OR LESS

Fig. 2. The range of cardiac indices in patients with liver disease and extrahepatic obstruction (E.H.O.). The portal-systemic collateral circulation is graded zero (absent), one plus (moderate), two plus (marked) and P.C.A. (surgical portacaval anastomosis).

# RESULTS

Cardiac Output. The mean cardiac index of the control group was  $3.68 \pm 0.60$  L./minute/sq. M. This value closely approximates the means of several normal series obtained by the Fick and dye methods [2]. In portal cirrhosis, the mean cardiac index was  $5.36 \pm 1.98$  L./minute/sq. M. The range was wide but approximately one-half the results were above the upper limit of normal. (Fig. 1.) There was a significant difference (p < 0.01) between the cardiac indices of the normal subjects and the group with portal cirrhosis. In contrast, in biliary cirrhosis the mean cardiac index of  $3.97 \pm 0.75$  L./minute/sq. M. did not differ significantly from the normal group (0.4 .

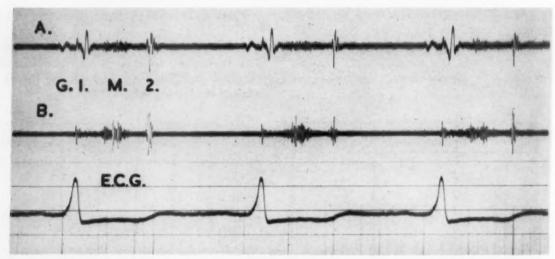


Fig. 3. Phonocardiogram from a patient with high cardiac output and portal cirrhosis. A, low frequency record; B, high frequency record; E.C.G., (electrocardiogram) lead II—showing: 1, first heart sound; 2, second heart sound; M, ejection type systolic murmur; and G, presystolic gallop.

A partial correlation [77] of cardiac index, hematocrit and serum albumin was made. This showed no significant correlation between cardiac index and hematocrit after correcting for the effect of serum albumin alterations (r = -0.27); only three patients had hematocrits less than 30 per cent. A better correlation was found between cardiac output and serum albumin after correcting for hematocrit changes (L = -0.36); this is not statistically significant (0.1 < p < 0.2) but may indicate a trend.

In the patients with liver disease, a statistically significant (p < 0.05) correlation was found between the cardiac index and the presence and magnitude of a portal-systemic collateral circulation. (Fig. 2.) However, the cardiac output of six patients with extrahepatic portal vein obstruction and an extensive portal-systemic vascular bed did not differ from the controls. Although all patients with portal cirrhosis and an elevated cardiac output had an increased portal systemic collateral circulation or a portacaval anastomosis, a similar collateral network without liver disease was not associated with a raised cardiac output.

In general, patients with portal cirrhosis and a high cardiac output had ejection systolic murmurs, often associated with a diastolic gallop (Fig. 3), wide pulse pressure, low mean arterial pressure and low peripheral vascular resistance. (Table I.) Clubbing was noted in seven patients with portal cirrhosis and all but one had a cardiac index greater than the upper limit of normal (4.87 L./minute/sq. M.). On the other

hand, clubbing was found in four of six patients with biliary cirrhosis, all with a normal cardiac output.

In all patients with liver disease the cardiac index was significantly greater in patients with angiomas compared to patients without nevi (p < 0.05). (Fig. 4.) No significant difference was noted when only the patients with portal cirrhosis with and without angiomas were compared (0.3 ); however only four patients with portal cirrhosis were free of angiomas. There was no difference in the cardiac indices between patients with one to five angiomas (one plus) and subjects with six or more spider nevi (two plus); many of the "two plus" patients had florid large pulsating angiomas. A similar lack of correlation was found between liver palms and cardiac output.

In spite of the frequently abnormal circulatory state in patients with portal cirrhosis, only two patients had cardiac enlargement by roent-genography (Cases 17 and 38). Electrocardiograms revealed a left ventricular hypertrophy pattern in two patients (Cases 29 and 44), right ventricular enlargement in one instance (Case 17) and an old myocardial infarction in the oldest patient of the group (Case 28).

Blood Volume. The mean blood volume in patients with portal cirrhosis was significantly elevated compared to the control subjects (0.01 . Most of the increase was in the plasma volume fraction with slight change in the red cell mass. (Table II.) In contrast, the blood volume of the patients with chronic biliary

Table 1
SUMMARY OF CLINICAL AND LABORATORY FINDINGS
(NUMBERS WITHIN PARENTHESES INDICATE RANGE OF FINDING)

CIII	culatory Changes in Chrome	LIVE	I Discuse 11		,	
Blood	180/80 120/70‡ 143/73 128/80 110/58 135/64 99/52 98/52 105/74 133/75 130/80‡ 110/52 110/65		110/57 125/76 123/69 119/61 134/76 104/51		143/72 149/89 160/80 149/69 130/80‡	
Arterial Oxygen (% saturation)	94.0 994.6 99.0 99.0 93.2 97.5 97.5 96.3 96.3 96.3		97.7 97.6 96.3 95.7 92.4 95.5		95.6 98.1 95.1 96.7 96.4	
Blood volume (L./M²)	4.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0		80888668		322233	
Cardiac Index (L./m./ M²)	886644444486044666 66488106404611606		0.0004.00 0.0004.00		&&&&&&4 &&1√&±8	dice.
Hema- tocrit (%)	30.0 31.5 31.5 31.5 31.5 31.5 32.0 34.5 34.5 34.5 34.5 34.5 37.5 37.5 37.5 37.5		39.0 39.8 39.0 34.4 39.9 24.2		39.5 29.6 33.8 31.2 36.5	azine jaun
Portal- Systemic Collaterals (0-2)	**************************************	sis	::::::		00000	Chlorpromazine jaundice.
Edema (0-2)	01000000-010000010	Anastomo	00====0		000000	50
Ascites (0-2)	0001100100100	Portacaval	0000000	Biliary Cirrhosis	000000	ter readin
Palpable Spleen (0-2)	100111000071100	Portal Cirrhosis with Portacaval Anastomosis	0	Biliary	00	Sphygmomanometer reading.
Mur- murs (0-4)	00000110001100	Portal Cir	помими		00000	‡ Sphygn § Wilson
Club- bing	0000000000000		00-00		101101	
Vascular "Spiders" (0-2)	-000-000-0100-01		1000100		00000-	or autopsy
Surface Area (M²)	1.76 1.62 1.84 1.80 1.81 1.71 1.71 1.74 1.74 1.54 1.55 1.56 1.65		1.65 1.49 1.72 1.86 1.91 1.37		1.52 1.62 1.44 1.27 1.52	olenogram
Duration of Symptoms	12 mo. 18 mo. 6 mo. 11 yr. 3 yr. 18 mo. 6 yr. 5 mo. 4 yr. 4 yr. 6 yr. 6 yr. 7 yr. 6 yr. 7 yr. 7 yr. 8 yr. 9 yr. 11 yr. 9 yr. 11 yr. 11 yr. 11 yr. 12 yr. 13 yr. 14 yr. 17 yr. 18 yr. 18 mo. 11 yr. 18 mo. 11 yr. 12 yr. 13 yr. 14 yr. 15 mo. 17 yr. 18 yr. 18 yr. 18 yr. 18 yr. 18 yr. 18 yr. 18 yr. 19 yr. 10 yr. 10 yr. 11 yr. 12 yr. 13 yr. 14 yr. 16 yr. 17 yr. 17 yr. 18 yr. 18 yr. 18 yr. 19 yr. 10 yr. 10 yr. 11 yr. 12 yr. 12 yr. 13 yr. 14 yr. 17 yr. 17 yr. 18 yr. 18 yr. 18 yr. 19 yr. 10 yr. 10 yr. 11 yr. 11 yr. 11 yr. 12 yr. 12 yr. 13 yr. 14 yr. 17 yr. 17 yr. 17 yr. 18 yr		33. yr. 2 yr. 5 yr. 23.2 yr. 4 yr.		5 yr. 4 yr. 12 yr. 18 mo. 6 yr.	Hemochromatosis. Confirmed by surgery, splenogram or autopsy
Sex	KKTZKTTTTTTK		FFZZFFZ		Zrrrrr	nrome
Age	55 445 445 36 669 669 669 70 70 70 70 70 70 70 70 70 70 70 70 70		17 57 47 47 56 49		63 50 71 29 53	Hemochromatosis.
Case No.	122 * 4 3 3 5 7 1 1 1 2 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1		18 % 20 21 22 22 23 24 24		25 26 27 28 29	* +

cirrhosis and extrahepatic portal vein obstruction did not significantly differ from the normal group. (Fig. 5.)

In general, elevated blood volumes were found in portal cirrhosis patients having: (1) an elevated cardiac output, (2) an extensive portal with extrahepatic portal vein obstruction had blood volumes mainly within the normal range. This observation does not support the view that the increased volume of the venous collateral bed is largely responsible for the elevated total blood volume found in patients with Laennec's cir-

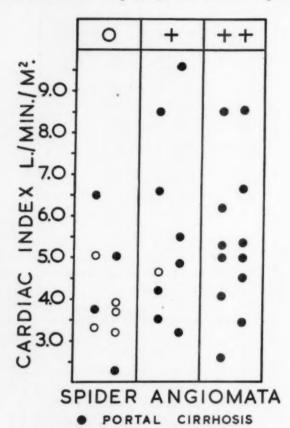


Fig. 4. Correlation of cardiac index and spider angiomas in all patients with liver disease; no spider angioma (zero), one to five angiomas (one plus) and six or more angiomas (two plus).

BILIARY CIRRHOSIS

collateral circulation, (3) arterial desaturation, and (4) decreased serum albumin levels. Patients with an elevated cardiac index had a significantly increased blood volume when compared to the normal group (p < 0.01), but this was only of borderline significance (0.05 < p < 0.1) when compared to the remaining patients with portal cirrhosis and a normal output.

Patients with liver disease and a demonstrable portal-systemic collateral circulation (Fig. 6) had a significantly greater blood volume (0.02 < p < 0.05) than patients with liver disease without a portal-systemic shunt. The presence of the collateral network itself is not responsible for the increased blood volume because the patients

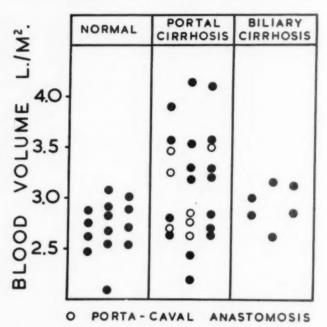


Fig. 5. The range of blood volume in normal adult subjects and in patients with portal cirrhosis and biliary cirrhosis. Normal =  $2.72 \pm 0.25$  L./Sq. M. Hollow circles represent patients with portacaval anastomosis.

rhosis [7,18]. Portacaval anastomosis decreased the collateral network yet the blood volume is increased; this is further evidence against an increased volume of the splanchnic venous system being the main cause of the elevated total blood volume.

There was no statistical difference between the blood volume of portal cirrhotic patients with and without fluid retention (0.3 . A similar lack of correlation between blood volume and ascites or edema in cirrhosis has been noted by Eisenberg [8] and Hiller, Huffman and Levey [18].

Low serum albumin levels are generally found in patients with high blood volumes (Fig. 6); this may represent, in part, dilution of a normal amount of circulating albumin. A similar dilution mechanism accounted for approximately 50 per cent of the low serum albumin levels in patients with cirrhosis studied by Hiller et al. [18].

Arterial Oxygen Saturation. Four of the twentyfour patients with portal cirrhosis had an arterial

oxygen saturation below the lower limit of normal (94 per cent saturated) and in the three patients studied further, the arterial blood did not become fully saturated after breathing 100 per cent oxygen for fifteen minutes. (Table III.) This favors a systemic venous to arterial shunt [19].

Table II
THE BLOOD VOLUME IN PATIENTS WITH LIVER DISEASE
AND EXTRAHEPATIC PORTAL OBSTRUCTION (E.H.O.)

	Normal	Portal Cirrhosis	Biliary Cirrhosis	E.H.O
Total Blood Volume L./M²				
Mean	2.72	3.13	2.93	2.89
S.D	0.25	0.52	0.21	0.39
No. of patients	14	24	6	6
Plasma Volume L./M²				
Mean	1.69	2.08	2.00	1.83
Standard Deviation	0.11	0.49	0.08	0.25
Red Cell Mass L./M <sup>2</sup>				
Mean	1.03	1.05	0.93	1.06
Standard Deviation	0.22	0.26	0.16	0.17

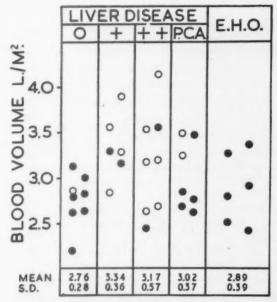
TABLE III
THE HEMATOCRIT AND RED CELL MASS OF THREE PATIENTS
WITH HEPATIC CIRRHOSIS AND ARTERIAL OXYGEN
DESATURATION

		,	
	,	Hema- tocrit	Red Cell Mass
Resting	After Oxygen*	(%)	L./M <sup>2</sup>
93.2	96.6	42.7	1.41
84.7	94.2	51.0	1.84
92.4	96.9	49.8	1.24
97.0	100.0	45.0	1.03
	93.2 84.7 92.4	93.2 96.6 84.7 94.2 92.4 96.9	Saturation (%)  Resting After Oxygen*  93.2 96.6 42.7 84.7 94.2 51.0 92.4 96.9 49.8

<sup>\*</sup> Saline manometer.

Evans blue dye curves performed during catheterization [20] in two patients showed no evidence of an intracardiac right to left shunt. It seems likely that these patients had a pulmonary arteriovenous shunt. Wilson and coworkers [21] calculated small pulmonary arteriovenous shunts of unknown variety in patients with cirrhosis. Rydell and Hoffbauer have described a patient with cirrhosis and multiple pulmonary arteriovenous fistulas [6]. We have studied a similar patient reported in detail in the next section.

The red cell mass was increased in three of the four patients with arterial desaturation. Two of four patients with low arterial oxygen saturation and portal cirrhosis had clubbing of the fingers. The frequent association of digital clubbing with biliary cirrhosis was not related to peripheral arterial desaturation although many of the patients appeared cyanotic.



SERUM ALBUMIN > 3.0 GMS. %
 SERUM ALBUMIN 3.0 GMS. % OR LESS

Fig. 6. The range of blood volumes in patients with liver disease and extrahepatic obstruction (E.H.O.). The portal-systemic collateral circulation is graded as in Figure 2.

#### CASE REPORTS

Two cases are reported as extreme examples of heart disease associated with portal cirrhosis.

CASE 1. Portal cirrhosis with hyperkinetic circulation and congestive heart failure: This fifty-one year old white man had been a chronic alcoholic for many years. Congestive cardiac failure had been present for eight months and had progressed in spite of dietary therapy and intramuscular administration of thiamin.

He was admitted to Hammersmith Hospital markedly orthopneic and in frank congestive failure. He was mildly icteric without cyanosis or clubbing. The hands were warm and moist and the peripheral pulses were full and bounding, with a blood pressure 170/80 mm. Hg and pulse rate of 120 per minute. He had a single angioma on his lip. The jugular veins showed a prominent A wave and were distended to the mandible with the patient sitting upright. An active apex impulse was felt 1 to 2 cm. to the left of the mid-clavicular line in the 5th intercostal space. A loud blowing systolic murmur was heard in the tricuspid and pulmonary areas; in addition there was a loud protodiastolic gallop. Massive ascites and lower extremity and sacral edema were present.

Urinalysis showed only a trace of protein. Investigations showed hemoglobin 9.3 gm. per cent, hematocrit 28.0 per cent, leukocytes 19,000 per cu. mm., serum albumin 2.5 gm. per cent, serum globulin 3.5 gm. per cent and serum bilirubin 2.3 mg. per cent. The electrocardiogram was normal and the

Table IV
THE BLOOD VOLUME AND CARDIAC OUTPUT OF PATIENT
BEFORE AND AFTER TREATMENT

Date	Cardiac Output (L./ min.)	Peripheral Resistance (Dynes sec. cm8)	Mean Arterial Pressure (mm. Hg)	Blood Volume (L./ M.²)	Central Venous Pressure (mm. Hg)
March 7, 1956. March 12, 1956	15.0	610 910	115 110	4.14	32/-1 13.2*

<sup>\*</sup> Saline manometer.

roentgenogram of the chest revealed questionable cardiac enlargement and marked pulmonary congestion.

Five days later limited cardiac catheterization showed the right atrial pressure to be 32/-1 mm. Hg (mean 14 mm. Hg), the cardiac output 15.0 L./minute, the mean arterial pressure 115 mm. Hg, and the calculated peripheral resistance 610 dynes second cm.<sup>-5</sup>. Digitalis, mercurials and a low salt diet were administered with marked improvement and a 9 pound weight loss due to diuresis. Subsequent study when the patient had improved clinically revealed a considerable fall in cardiac output and blood volume, an increase in peripheral resistance and a fall in the central venous pressure. (Table IV.)

The congestive failure improved over the next six weeks although he continued to show evidence of a hyperdynamic circulation. However, his liver function suddenly failed and he died following a gastro-

intestinal hemorrhage.

Postmortem examination confirmed the presence of chronic portal cirrhosis and esophageal varices. The heart weighed 425 gm. There was slight dilatation and moderate increase in thickness of the left ventricular wall (19 mm.). All valves were normal and the coronary arteries and aorta showed minimal atherosclerosis. Histologically the myocardial fibers were slightly increased in size but showed no other abnormality; no fibrosis or infiltration was seen.

This patient was the only one seen with congestive heart failure. No cause for heart failure could be adduced other than the high output state associated with chronic liver disease.

CASE 17. Portal cirrhosis and multiple pulmonary arteriovenous fistulas: This twenty-five year old white man had prolonged fever and jaundice (infectious hepatitis) at the age of four. He was well and active until fourteen years of age when he noted gradual

onset of weakness and exertional dyspnea. Since the age of sixteen, multiple episodes of hematemesis or melena had occurred, requiring transfusions on two occasions, and at the age of sixteen he underwent splenectomy for splenomegaly with anemia and thrombocytopenic purpura. At operation the liver was nodular, and biopsy showed portal cirrhosis. For the past year exercise tolerance had become increasingly limited and he has been unable to work. He has had no nocturnal dyspnea, orthopnea, chest pain or ankle swelling.

Physical examination showed a young man with slightly clubbed fingers, cyanotic mucous membranes and nail beds, and a few spider angiomas. Blood pressure (120/70 mm. Hg) and venous pressure were normal. The thorax was enlarged in the A-P diameter. The heart appeared slightly enlarged. The second heart sound in the pulmonary area was slightly split and accentuated. No murmurs or abnormal sounds were heard over the heart or lungs. The liver was not palpable. The peripheral pulses were full and bounding and the extremities were warm.

Laboratory studies revealed the following: hematocrit 51 per cent, hemoglobin 14.2 gm. per cent, serum albumin 3.3 gm. per cent and globulin 3.6 gm. per cent. The electrocardiogram showed right ventricular hypertrophy and roentgenograms of the chest revealed normal lung fields, right ventricular enlargement and dilatation of the main pulmonary artery. No esophageal varices were found on barium swallow.

On cardiac catheterization, the femoral arterial oxygen saturation was 84.1 per cent rising to 94.2 per cent after breathing 100 per cent oxygen. The cardiac index was 4.93 L./minute/sq. M. Analysis of oxygen content of samples obtained from the vena cavae, right atrium, right ventricle and pulmonary artery showed no evidence of a left to right shunt. Evans blue dye studies from the pulmonary artery, right atrium and superior vena cava gave no indication of an intracardiac right to left shunt. The main pulmonary artery pressure was 44/26 (mean 34) mm. Hg. The calculated total pulmonary vascular resistance was 655 dynes second cm.-5. Subsequent angiocardiography failed to show an intracardiac shunt or to localize a pulmonary arteriovenous anastomosis. Pulmonary function studies were normal. The plasma volume was 3,958 ml. and the total blood volume

This young man with posthepatitis cirrhosis suffered from multiple small gastrointestinal hemorrhages and more recently from an increasingly limited exercise capacity. Cardiac catheterization and pulmonary function data strongly suggested that the arterial desaturation was due to a right to left shunt at the pulmonary arterial level, probably from multiple pulmonary arteriovenous anastomoses. The cause of his modest pulmonary hypertension and increased pulmonary vascular resistance remains unknown. Right ventricular hypertrophy was also noted in a

similar patient described by Rydell and Hoffbauer [6].

#### COMMENTS

The patients studied are not representative of all cases of portal cirrhosis. Patients were deliberately selected with hyperkinetic circulatory states, extensive collateral circulation, clubbing or cyanosis. The results obtained cannot be applied to liver disease as a whole and the frequency of circulatory changes is unknown. However, certain conclusions can be drawn.

The presence of a high cardiac output in chronic portal cirrhosis has been confirmed. Previous reports have dealt with cirrhosis in alcoholic patients [2,22]; we have observed in cirrhosis of other etiologies a hyperkinetic circulation that could not be related to anemia or nutritional deficiencies.

It is difficult to separate the features involved in the production of a hyperdynamic circulation. The mild liver damage and jaundice of biliary cirrhosis without demonstrable portal collateral circulation, and extrahepatic portal vein obstruction with normal liver function did not lead to a hyperkinetic state. A high cardiac output has been noted in a patient with subacute hepatitis and liver failure who showed no portal collateral circulation at autopsy [23]. We have observed a similar patient with fulminating hepatitis who, without a change of blood pH, had a cardiac output of 15.0 L./minute with a normal blood volume and markedly lowered peripheral resistance. These findings suggest that some degree of liver failure is the essential factor but extrahepatic portal-systemic shunting of blood can be contributory. Further studies before and after portacaval anastomosis are indicated to clarify this point.

The elevated cardiac output with an increased total blood volume (mainly a raised plasma volume with a normal red cell mass) found in portal cirrhosis closely resembles that found with a systemic arteriovenous fistula [24,26], or the generalized vasodilatation of acute beriberi [27,28]. The opening up of a large number of normally present but functionally inactive arteriovenous anastomoses by a vasodilator substance is theoretically equivalent to the effects of a single arteriovenous fistula. Shorr has demonstrated the production of a vasodilator material by the diseased liver [29]. The failure of the diseased liver to metabolize a vasodilator substance produced elsewhere in the body or

absorbed from the gut is an alternative explanation to Shorr's hypothesis.

The association of increased cardiac output and a portal-systemic collateral circulation may represent merely two independent aspects of a progressive, chronic disease; or they may be more causally related, due to the shunting away from the liver of some vasodilator substance normally metabolized by the parenchymal cells. An analogous situation accounts in part for the decreased ammonium tolerance found in chronic liver disease [30].

Plethysmography [3] and calorimetric measurements [4] show an increased peripheral blood flow in chronic liver disease. Increased peripheral venous oxygen saturation in cirrhosis and hepatitis has also been presented as evidence of shunting of blood through arteriovenous anastomoses [31]. Whether or not the total increase in cardiac output is distributed to the periphery is unknown. If a vasodilator substance is present it might act generally and the increased flow be more apparent in the upper extremities due to the greater number of arteriovenous anastomoses in hands and forearms. A slight increase in splanchnic flow might therefore be expected. Although the hepatic blood flow is decreased in chronic liver disease [32] the volume and flow through the total splanchnic bed, including collaterals, remains unknown. A generalized vasodilation would accommodate the increased blood volume in the portal cirrhotic group. Neither of these is found in the patients with extrahepatic obstruction and, since a similar degree of collateral circulation is common to both groups, an additional factor is needed to explain the increased blood volume of the former group.

Multiple pulmonary arteriovenous fistulas associated with portal cirrhosis have been clearly demonstrated by Rydell and Hoffbauer [6] and our Case 17 is probably similar. The presence of pulmonary arteriovenous shunts adequately explains the initial arterial oxygen desaturation and failure to reach 100 per cent saturation following inhalation of 100 per cent oxygen in two other patients in this series. This phenomenon may also result from a vasodilator material acting particularly upon preformed pulmonary arteriovenous anastomoses.

In general, patients with an elevated cardiac output due to portal cirrhosis have a normal response to exercise [22] and tolerate the added circulatory burden without decompensation.

No reports were found in the literature similar to our Case 1 who had heart failure due to liver disease without associated thiamin deficiency. It is probable that most patients die of liver failure before congestive heart failure has had time to develop. It is known that a small to moderate sized systemic arteriovenous fistula may be present for many years before causing signs of congestive heart failure.

No specific therapy is indicated for patients with a hyperdynamic circulation unless decompensation is present. Observations in nine cases have shown that as liver function improves in the hospital the cardiac output returns toward normal. Therapy should be directed to improv-

ing the underlying liver disease.

#### SUMMARY

The circulatory findings in twenty-four patients with portal cirrhosis were compared with results in six patients with biliary cirrhosis, six patients with extrahepatic portal vein obstruc-

tion and fourteen normal subjects.

Half the patients with portal cirrhosis had a cardiac index above the upper limit of normal. Clinically, these patients had evidence of increased peripheral blood flow and ejection systolic murmurs. Roentgenographic or electrocardiographic changes were uncommon. Patients with biliary cirrhosis and portal vein obstruction had normal cardiac indices.

An increased total blood volume, mainly plasma volume, was found in patients with portal cirrhosis who had an increased cardiac index, a large portal-systemic collateral circulation, arterial oxygen desaturation and low serum albumin levels. The increased portal venous network did not account for the increased blood volume in portal cirrhosis as patients with extrahepatic portal vein obstruction had virtually normal blood volumes. The low serum albumin levels may in part represent the dilution of a normal amount of circulating albumin by an increased plasma volume.

Four patients had low arterial oxygen saturation. Cardiac catheterization data in one patient and studies in two others suggest that the arterial desaturation may be due to the shunting of blood through pulmonary arteriovenous anastomoses. One of these cases is presented in detail.

In most patients with portal cirrhosis the increased cardiac output was tolerated without evidence of decomposition. Congestive heart failure was present in one patient reported in

detail. As liver function and the clinical status of patients with portal cirrhosis improved, the cardiac output returned toward normal.

The mechanism of production of the hyperdynamic circulatory state in portal cirrhosis is unknown. There is profound vasodilatation and the mechanism of this is discussed.

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# The Problem of Increasing Azotemia During Management of Diabetic Acidosis\*

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In the patient with uncomplicated diabetic acidosis nitrogen retention of some degree is more the rule than the exception [1-4]. Dehydration plays a role, but elevation of the blood non-protein nitrogen inconsistent with dehydration alone is frequently seen, and it seems necessary in these cases to postulate some degree of complicating impairment of renal function.

In a majority of patients with uncomplicated acidosis and coma there is evidence of a transient disorder of renal function. Proteinuria may be present, and hyaline and granular casts and red blood cells are frequently found in the urinary sediment. Reubi [4] has studied the mechanisms of production of azotemia and showed an increase in blood viscosity and a sharp reduction in urea clearance, glomerular filtration rate, "effective" renal blood flow and "true" renal blood flow during diabetic coma. In eight of nine patients renal functions promptly returned to normal during the course of treatment. He interpreted his findings as indicating that slowing of renal blood flow due to increased blood viscosity accounted for the azotemia. This was supported by an inverse relationship between renal blood flow and blood viscosity during and after coma. The term "functional nephropathy" was used to describe the disorder of renal function in diabetic acidosis.

The magnitude of nitrogen retention varies widely but in general correlates with the severity of the acidosis and with the prognosis [5]. Prompt restoration of renal function to normal is the rule in the patient treated successfully [4,6,7]. Occasional patients have a persistent or increasing azotemia during the course of treatment, and when this occurs other causes of disordered renal function and azotemia may be responsible. *Infection* can precipitate diabetic acidosis and produce azotemia. At times the source of infection may not be apparent, and

persistent or increasing nitrogen retention may be a manifestation of its presence. Dramatic reduction in azotemia often accompanies the control of infection under these circumstances. Obstructive uropathy may produce severe azotemia during diabetic acidosis and is not uncommonly associated with infection. Preexisting chronic renal disease, such as glomerulonephritis, pyelonephritis and polycystic kidneys, may lead to the development of uremia during acidosis, and detection of these diseases may be difficult. Intercapillary glomerulosclerosis may contribute to azotemia during diabetic acidosis without producing evidence of impaired renal function prior to this event. Arteriolar nephrosclerosis can be more easily recognized as a source of azotemia because of the consistent association of hypertension, but the importance of its contribution to nitrogen retention may be difficult to evaluate. In addition to these and other obvious causes of persistent or increasing azotemia during the management of diabetic acidosis, an occasional patient may display this pattern without an apparent explanation.

The charts of 476 adult patients admitted to the Johns Hopkins Hospital one or more times in diabetic acidosis between the years 1934 and 1955 were reviewed. Three patients were found in whom increasing azotemia occurred during the management of an episode of acidosis and in whom a ready explanation for the nitrogen retention was not apparent. Twenty-one other patients showed persistent azotemia associated with infection or chronic renal disease.

# CASE REPORTS

CASE I. B. S. (J. H. H. 695155), a twenty year old white man, was admitted in diabetic acidosis on January 25, 1955, having been stuporous for about twenty hours. His past health had always been good, and the findings on examination in the Army one

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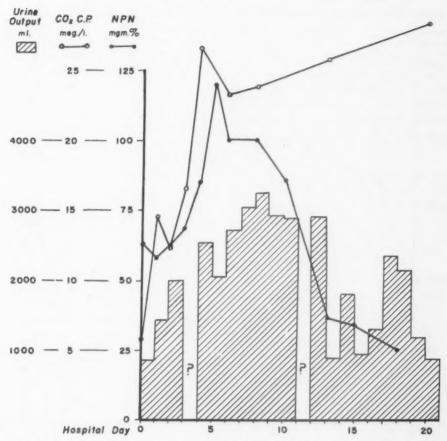


Fig. 1. Case 1. Changes in the serum NPN, CO<sub>2</sub> combining power and urinary output.

year earlier had been normal. One month before admission polydipsia and polyuria developed and he began to lose weight. Two days before admission he began to vomit and became quite weak.

The temperature was 96°F. (rectal); pulse, 104; respirations, 44 and Kussmaul in type. The blood pressure was 90/55 mm. Hg. The patient responded to painful stimuli. He was markedly dehydrated. The retinas were normal, and the lungs and heart showed no abnormalities. The remainder of the physical examination revealed nothing of importance.

The hematocrit was 48 per cent, white blood cell count was 18,000 per cu. mm. with a shift to the left, erythrocyte sedimentation rate (Wintrobe) was 35 mm. Urinalysis showed a specific gravity of 1.015, pH 6.0, protein, 2 plus; sugar, 4 plus; acetone, 4 plus; and a sediment containing many granular casts and occasional red and white cells. The non-protein nitrogen was 63 mg. per cent; blood sugar, 500 mg. per cent; CO<sub>2</sub> combining power, 6.9 mEq./L., serum chlorides, 106 mEq./L., sodium, 136 mEq./L.; and potassium, 4.6 mEq./L. The electrocardiogram was normal.

The hyperglycemia and ketosis were successfully controlled with insulin and intravenous fluids by the sixtieth hour. The blood pressure rose to 114/70

mm. Hg within the first two and a half hours. Intravenous potassium therapy was begun five hours after admission, and a total of 10 gm. of potassium chloride was administered over the next six hours. By the fourteenth hour after admission the patient was responsive, although respirations were still of a Kussmaul character. During the fifteenth hour there was an abrupt change in the patient's condition. A flaccid paralysis, shallow respirations and areflexia developed, and he became only barely responsive. His pulse was 80 and quite full, and blood pressure was 100/20/0 mm. Hg. An electrocardiogram showed typical changes of hypokalemia, confirmed by a serum potassium of 2 mEq./L. Over the next nine hours 20.5 gm. of potassium chloride were administered intravenously, for a total of 30.5 gm. within a nineteen hour period. The blood pressure gradually rose to 120/80 mm. Hg. At the end of this time the patient was alert and oriented, and remained so thereafter.

There was a progressive rise in the serum non-protein nitrogen to 120 mg. per cent on the fifth hospital day. (Fig. 1.) Phenolsulphonphthalein excretion on the fourth day was 25 per cent in two hours and on the seventh day, 30 per cent. Proteinuria persisted for four days, and serial urinalyses showed

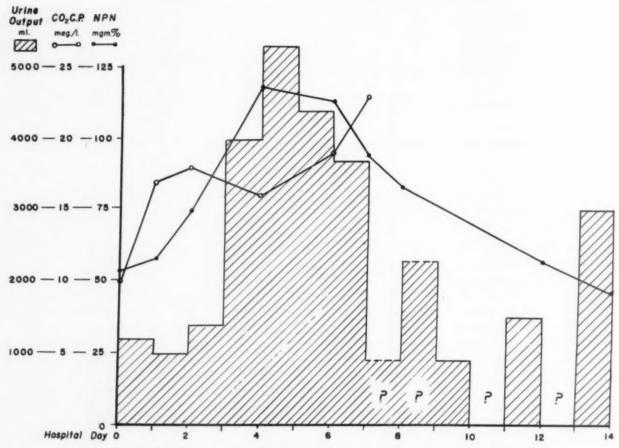


Fig. 2. Case II. Changes in the serum NPN, CO2 combining power and urinary output.

specific gravities fluctuating about 1.010 until the fifteenth day, when the specific gravity was 1.021. Cystoscopy and retrograde pyelography on the fifth day were normal. On the eighth hospital day the inulin clearance was 56 ml./minute (normal 130  $\pm$  20 ml./minute), and para-amino hippurate (PAH) clearance was 202 ml./minute (normal 700  $\pm$  135 ml./minute). One week later the inulin clearance was 92 ml./minute, and the PAH clearance was 390 ml./minute. Four months later the patient was doing well, his serum non-protein nitrogen was 37 mg. per cent, and urinalysis was normal.

Comment: This young man had had symptoms of diabetes mellitus for one month before he was admitted to the hospital in acidosis. The acidosis was not difficult to control with fluids and insulin, but severe hypokalemia developed, requiring 30.5 gm. of potassium chloride within a nineteen hour period. There was progressive azotemia during the first seven days, as well as other evidence of impaired renal function without significant oliguria. A gradual fall in the serum non-protein nitrogen and return of renal function toward normal then followed. No obvious cause of the disordered renal function was

detected. It seems likely that acute renal failure without more than transient oliguria was responsible for the progressive azotemia.

CASE II. M. R. (J. H. H. 660244), a sixty-three year old white man, was admitted in a comatose state on December 22, 1953. He had had diabetes mellitus for six years. Adherence to regulation with diet and insulin was poor, and diabetic acidosis had developed on two previous occasions. Nocturia had persisted since the onset of his diabetes. Nausea and abdominal cramps developed twelve hours before admission and he gradually became comatose.

The temperature was 93.8°F. (rectal); pulse, 120; respirations, 32 and gasping. The blood pressure was 66/40 mm. Hg. He was markedly dehydrated, but the skin was cool and clammy. The lungs were clear, and the heart was normal except for the tachycardia. Examination of the abdomen revealed no abnormalities. The remainder of the examination was normal.

The hematocrit was 43 per cent and fell to 35 per cent after hydration. The white blood cell count was 14,650 per cu. mm. but later became normal. Urinalysis revealed 3 plus proteinuria, 4 plus glycosuria and 4 plus reactions for acetone and diacetic acid. The specific gravity was 1.020, and the

sediment contained a few white cells and occasional granular casts. The serum non-protein nitrogen was 54 mg. per cent; blood sugar, 744 mg. per cent; CO<sub>2</sub> combining power 10.1 mEq./L.; serum chlorides, 109 mEq./L.; sodium, 128 mEq./L.; and potassium, 4.6 mEq./L. The serum acetone test was positive in a 1:4 dilution.

Intravenous norepinephrine was given for five hours but was not required after that time. Therapy with intravenous fluids and insulin proceeded concomitantly. The temperature gradually rose to 100.4°F. during the next twelve hours but was never abnormal thereafter. Penicillin and gantrisin® were given. Five hours after admission serum acetone was still present in a 1:4 dilution, but urine acetone was only 2 plus, and the reaction for diacetic acid was negative. The serum potassium never fell below 3.4 mEq./L., and supplemental potassium was not given. A phenolsulphonphthalein test on the second day showed 30 per cent excretion in two hours, and on the eleventh day, 38 per cent in two hours. Intravenous pyelography on the eleventh day demonstrated bilateral excretion, but concentration of the dye was poor. The serum non-protein nitrogen gradually rose to 118 mg. per cent on the fourth day in spite of a good urinary output. (Fig. 2.) Azotemia slowly subsided during the next ten days.

The patient was readmitted in acidosis four months later and at that time had gross pyuria and coliaerogenes bacilluria. The serum non-protein nitrogen was 69 mg. per cent on admission, 33 mg. per cent the following day, and remained normal thereafter. Phenolsulphonphthalein excretion was 62 per cent in two hours. In addition to therapy with fluids and insulin, penicillin and tetracycline were given. The patient was found to have a 250 ml. residual urine, and cystoscopy revealed trabeculation of the bladder and hypertrophy of the median bar. Transurethral resection of the prostate was performed.

On December 21, 1954, one year after his first admission, the patient was readmitted, comatose and in shock. He died three hours after arrival. Permission for autopsy was not obtained.

Comment: This sixty-three year old man was admitted in a state of coma and shock due to diabetic acidosis. Norepinephrine was required for five hours because of hypotension, but the urinary output was always adequate after the first few hours. Severe hypokalemia did not develop. Renal insufficiency was indicated by increasing azotemia over a four day period and impaired phenolsulphonphthalein excretion. On a subsequent admission for diabetic acidosis increasing azotemia did not occur and the phenolsulphonphthalein excretion was normal, although he was found at that time to have obstructive uropathy. The renal insufficiency on his

first admission was probably secondary to shock and renal ischemia.

CASE III. N. S. (J. H. H. 370418), an eighteen year old woman, was admitted in a stuporous condition on December 4, 1953. She had had diabetes mellitus for seven years and had been admitted on eight previous occasions with diabetic acidosis. She had been having mild diarrhea for seven days and in the twenty-four hours before admission malaise, anorexia, nausea and vomiting had developed.

The temperature was 99.4°F. (rectal); pulse, 104; respirations, 24 and of a Kussmaul character. The blood pressure was 144/90 mm. Hg. She was moderately dehydrated, and there were numerous excoriated secondarily infected areas on her extremities. Findings on examination of the chest, abdomen and pelvis were within normal limits.

The hematocrit was 49 per cent, white blood cell count was 11,500 per cu. mm. Urinalysis revealed a specific gravity of 1.005 with a trace of proteinuria, 3 plus glycosuria, and 4 plus reactions for acetone and diacetic acid. There were a few red and white cells and moderate numbers of granular casts, but subsequent urinalyses showed normal sediment and no proteinuria. The serum non-protein nitrogen was 39 mg. per cent, blood sugar, 410 mg. per cent; CO<sub>2</sub> combining power, 6.9 mEq./L.; and serum chlorides, 107 mEq./L. Blood and urine cultures were sterile, and stool cultures contained no pathogens.

The patient was treated with insulin and intravenous fluids and received terramycin® for the infected excoriations. The electrocardiogram showed changes suggestive of hypokalemia several hours after admission, and these changes persisted for six days. The serum potassium was 3.7 mEq./L. two hours after admission and was not repeated until the fifth hospital day, when it was 1.9 mEq./L. On the seventh hospital day the serum potassium was 3.1 mEq./L. and it did not subsequently fall below this level. At no time were symptoms of hypokalemia detected, and no supplementary potassium was given. On the second day the patient was responsive, and on the third day she was able to take a full diet. At this time the serum non-protein nitrogen had risen to 98 mg. per cent, and a pericardial friction rub was heard. (Fig. 3.) The phenolsulphonphthalein excretion in two hours was 30 per cent, as compared with 70 per cent eight months earlier. On the tenth day phenolsulphonphthalein excretion was 20 per cent and maximum urine specific gravity was 1.018, but the serum non-protein nitrogen had fallen to normal.

She was admitted twice subsequently with diabetic acidosis and infected excoriations, but the serum non-protein nitrogen was not elevated on either occasion. The phenolsulphonphthalein excretion in January, 1955, was 77 per cent in two hours, and maximum urine concentration was 1.023. She is doing well at the present time.

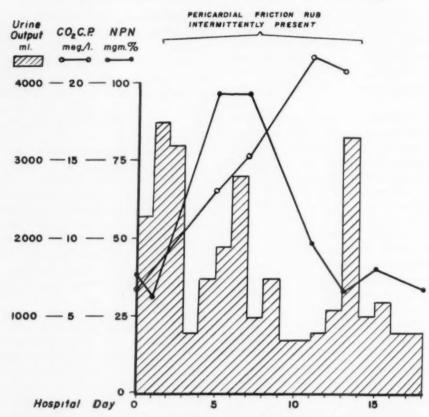


Fig. 3. Case III. Changes in the serum NPN, CO<sub>2</sub> combining power and urinary output, and occurrence of pericardial friction rub.

Comment: This eighteen year old woman had mild diarrhea for a week before admission with diabetic acidosis. Serial electrocardiograms showed changes suggestive of hypokalemia, and the serum potassium fell as low as 1.9 mEq./L., but there were no symptoms of hypokalemia, and supplemental potassium was not given. Renal insufficiency was indicated by increasing azotemia for four days and poor phenolsulphonphthalein excretion. A pericardial friction rub appeared concomitant with the rising serum non-protein nitrogen. The pattern of nitrogen retention was probably produced by acute renal failure without an evident oliguric phase.

## COMMENTS

In considering the problem of unexplained persistent or increasing azotemia during the management of diabetic acidosis it is at times difficult to exclude pre-existing chronic renal disease. This is particularly true of intercapillary glomerulosclerosis, the pathologic lesions of which may exist without diagnostic clinical features [8].

Infection and obstructive uropathy can cause

increasing azotemia but recognition of their presence is usually not difficult Appropriate treatment of infection and relief of obstruction may be followed by a dramatic decrease in the serum non-protein nitrogen level.

Among the suggested causes of unexplained renal insufficiency in diabetic acidosis have been the excretion of large amounts of ketone bodies, hypochloremia, and the use of large amounts of insulin during therapy [3]. None of these factors, however, seems to be of any major significance in the production of progressive azotemia during the treatment of acidosis. Ketone substances probably do not exert a direct injurious effect on the kidney [3], and ketosis is usually not followed by persistent impairment of renal function. Hypochloremia can also be dismissed, since it is not consistently present in patients displaying postcoma nitrogen retention. Hyperchloremia sometimes develops during therapy as a consequence of the employment of large amounts of normal saline solution and may contribute to the persistence of acidosis (so-called chloride acidosis) [9], but this also is not uniformly associated with postcoma nitrogen retention. The amount of insulin given during the treatment of diabetic

acidosis is usually proportionate to the severity of the process, but it is not always the most severely ill patient in whom persistent or progressive azotemia develops. In addition there is no evidence that insulin has any deleterious effect on the kidneys [3].

In the three cases presented it seems likely that the progressive azotemia was a manifestation of acute renal failure. There was no persistent oliguria in these patients, but acute renal failure without a striking oliguric phase has been described by others. Swan and Merrill [10] view this syndrome as representing a spectrum merging in one direction with functional renal disorders such as follow acute depletion of water and salt. Here renal function is usually rapidly restored by replacement therapy. Between such functional disturbances and overt acute renal failure are classified cases in which lingering impairment of renal function is revealed only by special tests. In such cases oliguria may be fleeting or undetected and azotemia transient.

The fundamental disturbance responsible for the development of acute renal failure in most cases is renal ischemia, and even in those cases due to metallic poisons ischemia plays a secondary role. Oligemia, hypotension and renal vasoconstriction lead to this reduction in renal blood flow [11]. (Acute renal failure may, however, occur in some cases without a detected period of hypotension.) In diabetic acidosis the degree of renal ischemia has been found to be proportionate to the increase in blood viscosity [4]. It would seem likely that acute renal failure would develop not infrequently in diabetic acidosis with its associated reduction in renal blood flow. Diabetic acidosis has, however, received little emphasis as a cause of acute renal failure and is not mentioned as an etiologic factor in several major reviews of the subject [10,12,13]. The reason for the apparent low frequency of acute renal failure in diabetic acidosis may be that the period of renal ischemia is usually not long enough to produce the overt manifestations of renal failure. The acidotic diabetic patient usually responds rapidly to treatment with consequent relief of renal ischemia or else succumbs in acidosis.

The mechanism of oliguria in acute renal failure is poorly understood and the source of much debate. Tubular back diffusion, renal ischemia, interstitial edema and tubular blockage are all mentioned as factors [12]. The means by which the diuretic phase is initiated are also obscure,

but severe abnormalities in renal function are still present when diuresis is initiated. It seems likely that abnormal tubular permeability, reduced glomerular filtration rate and reduced renal blood flow all persist in some degree [10]. Azotemia may continue to progress during the early diuretic phase, and a rising serum non-protein nitrogen over a period of several days may reflect a degree of acute renal failure after transient or undetected oliguria.

Acute renal failure secondary to renal ischemia in diabetic acidosis may have occurred in certain previously reported cases [3,4,7,14]. The possibility that it may occur in diabetic acidosis without an initial oliguric phase has been suggested by Bernstein, Foley and Hoffman [7]. They studied renal function during and after diabetic coma and found that their patients could be divided into two groups. In four patients renal functions returned to normal promptly, but two other patients had continued poor extraction of para-amino hippurate, isosthenuria and intensification of azotemia in spite of correction of acidosis and hyperglycemia. It was considered that the persisting abnormalities in these latter two patients were manifestations of acute renal failure, although an initial oliguric phase was not evident. An osmotic diuretic effect produced by hyperglycemia may be one factor in explaining the absence of initial oliguria in such patients.

A striking example of unexplained progressive but reversible azotemia in a young woman with diabetic coma, hypotension and hypokalemia has been reported by Kalinowski and Walker [14]. They do not speculate on the nature of the defect in renal function in their patient but the period of hypotension and the prolonged oliguria were suggestive of acute renal failure secondary to renal ischemia.

Alteration in the renal threshold for glucose and ketone bodies in diabetic acidosis with unexplained persistent or progressive azotemia gives further evidence of renal insufficiency in these circumstances. In the case reported by Kalinowski and Walker [14] there was an elevated threshold for glucose, and in Case II reported here the patient demonstrated a rise in the threshold for ketone bodies, as did one patient mentioned by McCance and Lawrence [3]. Coburn [15] found ketonemia without ketonuria in several patients with diabetic acidosis but, although he believed that this phenomenon was a warning of impending renal failure, its occur-

rence is not restricted to those patients in whom postcoma nitrogen retention develops.

The occurrence of renal dysfunction secondary to potassium deficiency has not been described in diabetic acidosis. Potassium depletion in diabetic acidosis is a relatively acute complication, but experimental potassium depletion in dogs results in polydipsia and polyuria within a few days [16], and changes in the renal tubular epithelium of rats are observed by the eighth day of such depletion [17]. It seems conceivable that renal dysfunction secondary to potassium depletion might develop in the occasional patient with diabetic acidosis when the magnitude of potassium loss is great and extends over a period of several days, as in Cases 1 and 111 reported here. A number of years ago Bayer [18] described histologic changes in the kidney compatible with potassium depletion in a patient dying during the management of diabetic acidosis. One of nine patients studied by Reubi [4] died with hypokalemia and was found to have granular and fatty degeneration of the proximal convoluted tubules with interstitial edema.

Assuming, however, that potassium depletion nephropathy may occur in an occasional case of diabetic acidosis it is unlikely that this could contribute significantly to the picture of nitrogen retention seen in our cases. Schwartz and Relman found the serum non-protein nitrogen to be normal or only slightly elevated in patients with potassium depletion nephropathy secondary to chronic diarrhea, although the glomerular filtration rate was reduced to less than half normal in one such patient [19,20]. The renal disorder in potassium depletion is chiefly one of tubular rather than glomerular dysfunction, and thus azotemia is never marked.

At this time the mechanism of the postacidotic azotemia which was observed in the patients reported here remains uncertain. When infection, obstruction and underlying chronic renal disease are excluded, cases of diabetic acidosis remain with unexplained increasing azotemia during the management of the acidotic episode. It seems possible that they may represent acute renal failure secondary to renal ischemia.

# SUMMARY

Most patients with severe diabetic acidosis have initial nitrogen retention of some degree. The mechanisms of this have been discussed. A few patients display unexplained increasing azotemia during treatment, although there is usually eventual complete restoration of renal function. Three of 476 patients having one or more episodes of diabetic acidosis were found to have unexplained progressive azotemia during the management of an acidotic episode. It is suggested that these patients may have had acute renal insufficiency without an evident oliguric phase.

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# The Fluid and Electrolyte Therapy of Severe Diabetic Acidosis and Ketosis\*

A Study of Twenty-nine Episodes (Twenty-six Patients)

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While much has been written concerning various forms of fluid therapy in the treatment of diabetic acidosis and ketosis, many problems have not been completely resolved in previously reported work. This study is an attempt to evaluate, with balance studies, various types of repair fluids.

#### MATERIAL AND METHODS

The twenty-six patients included in this study entered the Los Angeles County Hospital with serious diabetic acidosis and ketosis, all with serum bicarbonate levels below 9 mEq./L., with one exception in whom the serum bicarbonate was 10 mEq./L. Three patients were studied twice. There were sixteen women and ten men, with an age range from fourteen to seventy-three years. Serum sodium, potassium, calcium, magnesium, chloride, phosphate and bicarbonate levels were determined at two- to four-hour intervals during the period of intensive therapy, which was usually twelve hours. Urine samples were analyzed for electrolyte values synchronously with the serum levels in fifteen instances. Nine of these fifteen balance studies were complete, six incomplete. Blood ketone levels were determined at two to fourhour intervals in seventeen patients. The chemical methods used in the electrolyte and sugar determinations are those reported previously from this laboratory [1-7]. The urine electrolytes were measured by modifications of the methods employed for serum, except for urinary chloride which was determined by a modification of the standard Volhard-Arnold

In general, three types of fluids (hypotonic, isotonic and hypertonic) were used, with some variation between patients.

Schedule 1. 2 L. of 1/12 molar sodium lactate, and 3 L. "modified" Butler's solution. †

† The modified Butler's solution contained 57 mEq.

Schedule 2. 2 L. 1/6 molar sodium lactate and 2 to 3 L. 0.9 per cent saline solution.

Schedule 3. 2 L. combination of (34 L. 1/6 M sodium lactate) and (14 L. 0.9 per cent saline solution) and 3 L. Butler's solution.

Potassium chloride and potassium phosphate were given in varying amounts as indicated in the results. The potassium chloride was usually administered at the rate of 2 gm. per L. of any of the repair fluids used, starting with the second or third liter of intravenous fluid. The potassium phosphate solution was added at the rate of 1 ampoule per L. of repair fluid and given in varying total amounts as indicated in the results. Fourteen of the patients received phosphate solution.

All patients received 200 units of regular insulin intravenously every two hours until the blood sugar was below 300 mg. per cent, when smaller doses were given intramuscularly at two- to four-hour intervals. Dextran, plasma or whole blood and vasopressors were used for shock and decreased plasma volume, as required.

There were seven deaths in this series, a mortality of 24 per cent. Three of the deaths were clearly not due to the diabetic ketoacidosis. Autopsies were obtained in four instances.

#### RESULTS

Tonicity of Body Fluids in Diabetic Acidosis. 1. Calculated Osmolarity of Serum Prior to Therapy: Osmolarity or tonicity of the blood can usually be gauged by the serum sodium concentration, since the serum sodium level is the main force

Na, 50 mEq. Cl, 25 mEq. K, 21 mEq. PO<sub>4</sub>, 25 mEq.

lactate and 6 mEq. mg. per L. ‡ Each 5 cc. ampoule (Eli Lilly & Co.) contained 2 gm. K2HPO4 and 0.4 gm. KH2PO4.

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that governs movement of water between the extra- and intracellular compartments. In diabetic acidosis with hyperglycemia this is not true, as the osmolarity of the blood is significantly increased by the high blood glucose concentrations. Table 1 gives the initial cal-

Table 1

CALCULATED\* OSMOLARITY OF BLOOD ON ENTRY—

PER CENT OF TWENTY-FIVE PATIENTS

Normal Osmolarity	Increased Osmolarity	Decreased Osmolarity
32% (8 patients)	52% (13 patients)	16% (4 patients)
Range of osmolari	ty found (mOsm./L	.):
140-145.7	146.4-172.5	128.2-133

<sup>\*</sup> Calculated from serum sodium and glucose concentrations [8].

culated osmolarity of the serum in twenty-five patients: thirteen (52 per cent) had an increased osmolarity, eight (32 per cent) a normal osmolarity and four (16 per cent) a decreased osmolarity. If only the initial serum sodium level were considered (Table II) only 7 per cent of the patients would have shown an increased osmolarity, as 67 per cent of the initial serum sodium concentrations were low and 26 per cent within the normal range.

2. Effect of Therapy on Calculated Osmolarity of Serum at Twelve Hours: Figure 1 gives the calculated initial and twelve-hour serum osmolarity for the general type of fluid used.\* This figure shows that four of the seven patients receiving hypotonic fluid had a normal osmolarity and three an elevated osmolarity after twelve hours of therapy. In only one instance did the osmolarity rise during therapy. With the use of approximately isotonic fluid the calculated serum osmolarity was normal in one patient, low in one patient and elevated in three patients at twelve hours. In three instances there was a slight rise in osmolarity during therapy. When hypertonic solution was used (thirteen patients) the calculated twelve-hour serum osmolarity was normal in four, low in two and high in seven.

\* The glucose added to the intravenous solution is assumed to be administered relatively slowly and to be used rapidly, in view of the large doses of insulin given, therefore it is not calculated in the osmolarity of the fluid used.

In four instances there was a rise in osmolarity during treatment.

Increased osmolarity at twelve hours was associated with elevated serum sodium levels in nine of the thirteen instances in which it occurred. In one patient the increased twelve-hour

Table II
SERUM ELECTROLYTE LEVELS (PER CENT LOW, NORMAL OR
ELEVATED) AT ENTRY AND AFTER TWELVE HOURS
OF THERAPY (TWENTY-EIGHT PATIENTS)

		Entr	у	Tw	elve H	lours
Therapy	% Low	% Nor- mal	% High	% Low	% Nor- mal	% High
Sodium	67	26	7	26	41	33
Chloride	33	45	22	11	41	48
Bicarbonate	100	0	0	46	50	4
Calcium	28	68	4	73	23	4
Potassium	18	43	39	63	33	4
Magnesium	7	25	68	55	24	21
Phosphate	11	18	71	90	10	0

osmolarity was due to a high serum sugar concentration. In two patients there was a marked diuresis, probably due to a combination of a large glucose load and use of a very hypotonic fluid, resulting in a hypertonic contraction of the extracellular compartment. In one patient the increase in osmolarity was slight.

Retention of Fluid Correlated with the Use of Hypertonic, Isotonic and Hypotonic Fluids. One problem that concerned us was whether, in the face of loss of extracellular volume, hypotonic solutions would be retained as well as isotonic or slightly hypertonic solutions. This is an important consideration as it is urgent to restore the plasma volume to normal so that the kidneys will function at an optimum level.

Figure 2 shows the type and volume of fluid given as related to the volume of fluid retained in twelve hours in twenty-two patients. The average twelve-hour fluid intake was 4.49 L. (range 2 to 8.5 L.) with an average retention of the administered fluid of 69.6 per cent and an average twelve-hour urine volume of 1.29 L. (range 0.26 to 3.18 L.) It is to be noted that more fluid was retained at high intakes. At low levels of fluid intake a smaller amount is retained as there is an obligatory requirement of water for the urinary solute load. As the blood sugar levels

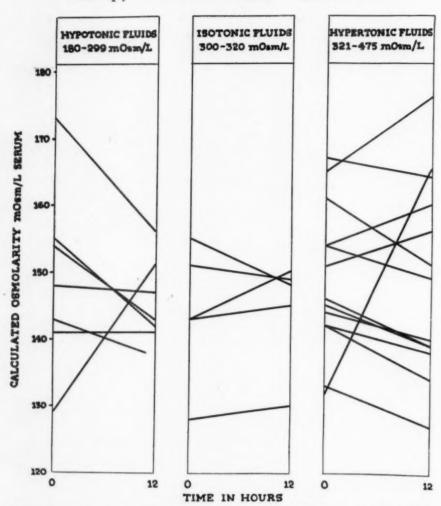


Fig. 1. Osmolarity of the serum in diabetic ketoacidosis correlated with tonicity of intravenous fluids administered.

and the solute loads to the kidney varied, it was difficult to analyze the effect of the tonicity of the fluid used on fluid retention. No clear cut difference in fluid retention with fluids of varying tonicity is noted, however. (Fig. 2.)

One patient was studied in three different episodes\* of severe diabetic acidosis and ketosis. (Table m.) Slightly less fluid was retained with the use of hypotonic fluid but the difference does not appear to be significant.

Correction of Acidosis. Nineteen of the twenty-eight patients (67.8 per cent) showed a twelve-hour rise of serum bicarbonate of 15 mEq./L. or more. Nine (32.2 per cent) had a rise of less than 15 mEq./L.

The average lactate intake was 329 mEq., chloride 305 mEq., with a lactate/chloride ratio of 1.08.

\* One of these episodes of severe ketoacidosis is not otherwise included in this paper.

If the nine cases in which there was a slower rise of serum bicarbonate are analyzed, the following factors, singly or in combination, were present: low lactate intake (under 250 mEq.), lactate/chloride intake ratio under 1, high entry and twelve-hour serum chloride level, and slow fall of the blood ketone level.

Serum Electrolyte Levels and Results of Balance Studies. Table II gives the entry and twelve-hour serum electrolyte levels in the twenty-eight patients followed for twelve hours. One patient died at six hours and so is not included in this table. Table IV gives the details of the balance study in one patient, Table v summarizes the results of the electrolyte balances during twelve hours of therapy in eight patients.

On entry 67 per cent of the serum sodium levels were low, 26 per cent normal and 7 per cent high. At twelve hours 26 per cent were low, 41 per cent normal and 33 per cent high. The sodium bal-

ance in eight patients during the first twelve hours of therapy is presented in Table v. The average sodium intake was 445 mEq., with an average retention of 92 per cent of the intake and an average urinary loss of 45 mEq.

On entry 33 per cent of the serum chloride levels were low, 45 per cent normal and 22 per

not entirely clear. One possibility is decreased renal function and poor urinary output of potassium. No correlation between non-protein nitrogen (or urea) level and serum potassium level was found in our series. Elevated serum non-protein nitrogen occurred in 70 per cent of the patients with both normal and elevated

TABLE III
RESULTS OF THREE DIFFERENT TREATMENT SCHEDULES IN
THE SAME PATIENT

(B. V. O., A TWENTY-THREE YEAR OLD WHITE WOMAN NO. 1143-592)

Hos- pital Ad- mis- sion	Four- hr. Vol- ume Intra- ve- nous Fluid (L.)	Four- hr. Urine Vol- ume (L.)	Fluid Given Re- tained (%)	Osmolarity of Intravenous Fluid (mOsm./L.)	Blood Sugar (0 to 4 hr.) (mg. %)
1	2.500	0.600	76	393	254-209
2	2.00	0.575	71	167	336-322
3	4.167	0.850	79.6	356	625-270

cent high (Table II) in contrast to the entry serum sodium levels. At twelve hours 11 per cent of the levels were low, 41 per cent normal and 48 per cent elevated. If the factors responsible for the rise in serum chloride are analyzed (Table VI) it is seen that they fall into the following categories: (1) a sodium and chloride intake in a ratio less than that in the serum (where it is 1:35 to 1:45); (2) a serum chloride level which was high prior to therapy; and (3) a rise of both serum chloride and sodium levels, due to use of hypertonic solutions with loss of more water than electrolyte. The average intake of chloride in eight patients was 240 mEq., with an average retention of 89 per cent of the intake and an average urine loss of 40 mEq. during the first twelve hours of therapy. (Table v.)

On entry 18 per cent of the serum potassium levels were low, 43 per cent were normal and 39 per cent were high. (Table II.) This is approximately the same range of percentages found in a much larger series—145 patients with severe diabetic ketoacidosis (unreported data), in which 15 per cent of the serum potassium levels were low, 45 per cent were normal, and 40 per cent were elevated on entry. The reasons for the variation in the serum potassium level on entry are

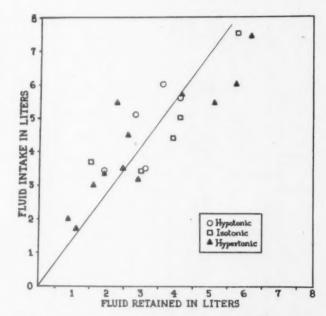


Fig. 2. The effect of tonicity of intravenously administered fluid on fluid retention in diabetic ketoacidosis.

entry serum potassium levels. There was no correlation between the entry serum potassium level and the hematocrit.

The balance study in eight patients (Table v) showed a range of potassium intake varying from 59 mEq. to 239 mEq., with an average intake of 145 mEq., with retention of 76 per cent of the intake, and an average urinary output of 41 mEq. At twelve hours 63 per cent of the serum potassium levels were under 4 mEq./L. (Table II), despite the average intake of 145 mEq.

Despite all instructions about cautious, slow administration of potassium, one patient received very large amounts of potassium rapidly and died of hyperpotassemia and acute respiratory failure. While the entry serum potassium level was known, subsequent changes in the electrocardiograms were interpreted as showing hypopotassemia. An additional important factor in the development of the hyperpotassemia here was the acidosis, which remained uncorrected as only 0.9 per cent saline solution was used. The large potassium load to the kidney

TABLE IV

			Sodium	Sodium Balance			CIIIO	Chloride Balance			Tariaic			Flu	Fluid Balance	9	
Time (hr.)	Type of Fluid Given Intravenously (L.)*	Intake (mEq.)	Urine (mEq.)	Balance (mEq.)	Serum Na (mEq./L.)	Intake (mEq.)	Urine (mEq.)	Balance (mEq.)	Serum Cl (mEq./L.)	Intake (mEq.)	Serum HCOs- (mEq./L.)	), L.)	Blood pH Venous	HsO Intake In- trave- nously	Urine (L.)	Balance (L.)	Serum Sugar (mg. %)¶
0 to 2 hr.,	1.375 L. of 1/12 M	114	20	+6+	131-131	40%	10	-10	110-108	114	<5-<5		7.12	1.375	0.750	+0.625	920-824
2 hr. 45 min. to 10 hr.	0.625 L. of 1/13 M Na lactate; 3 L. Butler's solution,† 4 amps.	223	32	+191	131–137	164	8	+161	108-110	127	<5-19		7.12-7.26	3.625	0.673	+2.952	824-282
10 to 13 hr.	KPO4,‡1 gm. KCL 0.63 L. Butler's solution,† 0.6 gm. KCl, 37 gm. glucose	36	61	+34	137-137	32	1	+31	110-107	16	19–23		7.26-7.36	0.63	0.120	+0.51	282-338
Total: 13 hr.		373	54	+319		961	14	+182	* * * * * * * * * * * * * * * * * * * *	257	•		* * * * * * * * * * * * * * * * * * * *	5.63	1.543	+4.087	
			Potassic	Potassium Balance	63		Phosphorus Balance	s Balance			Magnesium Balance	m Balanc	4)	Cal	Calcium Balance	ınce	
Time (hr.)	Type of Fluid Given Intravenously (L.)*	Intake (mEq.)	Urine (mEq.)	Balance (mEq.)	Serum K (mEq./L.)	Intake (mM)	Urine (mM)	Balance (mM)	Serum P (mM/L.)	Intake (mEq.)	Urine (mEq.)	Balance (mEq.)	Serum mg. (mEq./L.)	Intake (mEq.)	Urine (mEq.)	Balance (mEq.)	Serum Ca (mEq./L.)
0 to 2 hr.,	1.375 L. of 1/2 M	-	28	-28	7.42-4.2		25.0	-25	2.45-2.0	0	1.5	-1.5	2.35-2.05	0	1.5	-1.5	3.55-3.45
2 hr. 45 min. to 10 hr.	0.625 L. of M <sub>2</sub> M Na lactate, 3 L. Butler's solution, † 4 amp. KPO4, ‡	189	29	+160	4.2 -3.3	79.0	28.0	+51	1.57-1.8	90	2.5	+15.6	2.10-2.23	0	0.3	-0.3	3,45-3,45
10 to 13 hr.	1 gm. KCl 0.63 L. of Butler's solution, † 0.6 gm. KCl, 32 gm. glucose	. 24	٠	+18	4.1 4.5	4.0	9	1 2	1.8 -0.6	2	0.3	+1.7	2.33-2.17	0	0	0	3,45–3,15
Total: 13 hr.		213	63	+150		83.0	59	+24		20	4.2	+15.8		0	 - 00	8:1-	:

TABLE V
TWELVE-HOUR BALANCE OF ELECTROLYTES\*

		Sodiu	m			Chlor	ide			Potass	ium			Fluid	
Patient	Serum (mEq./L.) 0 to 12 hr.	Intake (mEq.)	Urine (mEq.)	Intake Re- tained (%)	Serum (mEq./L.) 0 to 12 hr.	Intake (mEq.)	Urine (mEq.)	Intake Re- tained (%)	Serum (mEq./L.) 0 to 12 hr.	Intake (mEq.)	Urine (mEq.)	Intake Re- tained (%)	Intake In- trave- nously (L.)	Urine Output (L.)	Fluid Given Re- tained (%)
R. W.† T. C. O. T.§ E. M.   L. G. L. H. M. P.¶ B. G.	130-143 136-147 131-137 122-158 138-137 138-140 124-134 115-124	394 374 373 784 366 372 492 404	35 8 54 228 8 13 6 8	91 98 86 71 98 97 90 98	92-99 117-119 110-107 74-114 98-101 107-104 107-111 94-115	227 144 196 728 112 117 199 197	44 13 14 210 5 11 2 23	81 91 93 71 96 90 99 88	6.6-4.43 3.98-2.73 7.0-4.36 2.01-4.21 5.3-3.91 4.37-2.93 3.4-3.7 2.67-2.9	239 67 213 186 59 91(78)? 122 180	77 8 63 59 18 27 16 19	68 88 70 68 69 70(65)? 87 86	6 3.5 5.63 5.45 3.17 3.40 5.45 4.47	2.365 0.487 1.543 3.180 0.260 0.310 0.295 0.550	61 86 71 42 92 91 95 88
Average		445	45	92		240	40	89		145 or 143	41	76	4.63	1.124	78
		Magnesiu	m			Calciu	ım			Phosph	ate		В	icarbonat	e
Patient	Serum (mEq./L.) 0 to 12 hr.	Intake (mEq./L.)	Urine (mEq.)	Intake Re- tained (%)	Serum (mEq./L.) 0 to 12 hr.	Intake (mEq.)	Urine (mEq.)	Intake Re- tained (%)	Serum (mEq./L.) 0 to 12 hr.	Intake P mM	Urine P mM	Intake Re- tained (%)		Serum mEq./L.) to 12 hr.	
R. W.† P. C. D. T.§ S. M.   J. G. H. M. P.¶ S. G.	1.88-1.65 1.85-1.30 2.35-2.23 2.27-1.38 1.07-0.87 1.86-1.51 1.98-1.84 1.7-1.56	24 5 20 0 4 5 9 8	3.5 1 4.2 1 1.5 1	85 80 79  63 80 89 88	4.5-3.6 4.5-4.10 3.55-3.15 4.3-3.7 3.6-3.6 4.4-3.9 3.85-3.7 4.8-3.7	0 0 0 0 0 0	2 1.15 2 6.1 1.0 2 1 0.5		2.6-1.22 1.62-0.85 4.41-1.09 4.43-0.72 1.58-0.23 1.75-1.59 1.84-0.89 1.45-1.92	86 or 71 32 83 14 or 0 29 31 11 62	16 ‡ 59 12 5 6 4 3	81 or 77 29 83 81 64 95		5-26 8-22 <5-23 8-26 7-23 8-25 8-24 6-18	
verage		9.4	1.8	81						44 or 47	15	72		****	

\* Fluid and electrolyte intake interpolated to hour of urine collection.

† Entry urine probably included in balance.

Interference in test with cloudy filtrate (two to six hours). Output hour: zero to two and six to twelve hours—2 mM.

§ Thirteen hours of intravenous fluid and urine collection started 2 hours before insulin Rx.

Thirteen hours

¶ Some question about urine volume, two to four hours whether 50 or 150 ml. Urine collection twelve and one-half hours.

thus had to compete with hydrogen ion for exchange in the tubules.

Another facet of the potassium problem which has never been raised previously is whether or not a very low serum potassium level and serious cellular depletion may not contribute to the polyuria. We have seen a few patients who have had very large urine volumes which could not be explained on the basis of either a large fluid intake or a large amount of urinary sugar. Patient E. M. (Table v) had a serum potassium of 2.01 mEq./L. on entry and a level of 1.54 mEq./L. at the end of two hours of therapy. In thirteen hours the urine output was 3.8 L., with an intake of 5.45 L. Is this the polyuria of potassium depletion, due to changes in the distal tubular epithelium [9]?

On entry 7 per cent of the serum magnesium levels were low, 25 per cent were normal and 68 per cent were elevated. At twelve hours 55 per cent were low, 24 per cent normal and 21 per cent were high. (Table II.) Similar results in a smaller series of patients had been reported previously from this laboratory [10].

In the seven patients who received magnesium, 4 to 24 mEq. (Table v), there was retention of 63 to 89 per cent of the administered magnesium. The sixteen patients who received no magnesium in the first twelve hours of therapy\* had an average fall in serum magnesium level of 0.66 mEq./L., while the thirteen patients who received magnesium had an average fall of the serum magnesium level of 0.33 mEq./L.

\* One patient was followed up for only 6 hours.

TABLE VI
HYPERNATREMIA AND HYPERCHLOREMIA AT TWELVE HOURS

Patient	Serum Na (mEq./L.) 0 to 12 Hr.	Serum Cl (mEq./L.) 0 to 12 Hr.	Na Intake 12 Hr. (mEq.)	Cl Intake 12 Hr. (mEq.)	Na/Cl Intake Ratio	Osmolarity Fluid Given (mOsm./L.)	Fluid Retained (L.)	Fluid Given Retained (%)
N. R.	129–149	94-119	708	647	1.1	406	(?)	(?)
E. M.	122-158	74-114	784	728	1.1	376	2.27	51
B. G.	115-124	94-115	404	197	2.1	319	3.90	87
T. C.	136-147	117-119	374	144	2.6	311	3.13	86
F. P.	139-172	107-132	906	682	1.3	350	4.13	72
F. T.	137-150	95-113	487	263	1.85	374	1.60	52
S. C.	126-126	112-121	371	377	0.99	408	1.90	56
B. V. O.	150-157	111-125	720	509	1.4	366	2.60	59
O. P.	143-172	112-129	604	229	2.6	295	2.80	54
J. H.	146-148	90-93	532	451	1.2	312	4.11	82
R. A.	121-148	102-106	627	208	3.0	235	(?)	(?)
M. P.	124-134	107-111	492	199	2.5	370	5.10	94
E. B.	131-140	(?)-111	385	128	3.0	302	2.23	40

Only seven of the patients who received magnesium had urine magnesium determinations.

Table II shows that 28 per cent of the serum calcium levels were low on entry, 68 per cent normal and 4 per cent high. At twelve hours, 73 per cent were low, 23 per cent normal and 4 per cent high. The urinary calcium output during the first twelve hours of therapy (Table v) ranged from less than 0.5 mEq. to 6.1 mEq. No patients were given calcium intravenously. When phosphate was given there was no greater change in the serum calcium or urinary calcium output than when no phosphate was given. (Tables IV and V.)

In Table II it is seen that 11 per cent of the initial serum phosphate levels were low, 18 per cent normal and 71 per cent elevated, some to very high levels. The serum levels fell precipitously in most instances by the fourth to eighth hours, so that at twelve hours 90 per cent of the levels were low. (Table II.) The reasons for the elevation of the serum phosphate on entry are not entirely clear, but might include decreased renal clearance secondary to dehydration, in addition to increased tissue breakdown. Further, high blood sugar levels and failure of glucose transfer into the cells, with accompanying lack of phosphate transfer, might be another factor. On analysis of our results no definite correlation with serum sugar levels could be established. There was only suggestive but no conclusive correlation with elevation of the non-protein nitrogen or urea levels, and elevation of the hematocrit.

Fourteen patients received intravenous phosphate therapy but in only seven of these patients was the urine collection for phosphate determination complete. These seven patients (Tables IV and V) received 11 to 86 mM. of phosphorus, with retention of 29 to 95 per cent of the amount administered. The difference in retention may well be related to the serum level and rate of phosphate infusion, as in some instances the phosphate clearances were very high, and fell rapidly when the serum level dropped below normal. The phosphate clearance in one patient (Table IV) was very high (27 to 67 cc./minute) during the period of high serum levels and high phosphate intake.

The serum phosphate levels in representative patients during the first twelve hours, with and without phosphate therapy, are shown in Figure 3. In general the serum levels were higher when phosphate was administered.

All of the serum bicarbonate levels were low on entry (due to selection of patients). At twelve hours (Table II) 46 per cent were below 25 mEq./L., 50 per cent were normal and 4 per cent were elevated. The average lactate intake (bicarbonate precursor) was 329 mEq. Urinary bicarbonate excretion was not measured but would be assumed to be negligible, due to the acidosis.

Blood ketone levels were estimated in seventeen patients, with entry levels ranging from 89 to 225 mg. per cent. At twelve hours the levels ranged from 7 to 188 mg. per cent. Figure 4 shows graphically the entry and twelve-hour

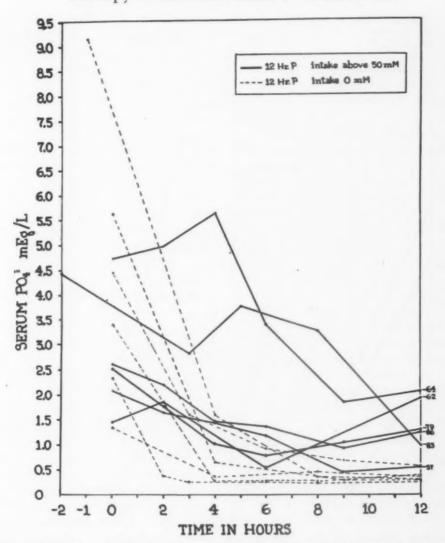


Fig. 3. Effect of phosphate\* therapy on serum phosphate level in diabetic ketoacidosis.

blood ketone levels in these patients, divided on the basis of sugar administration. The differences in rate of fall of the blood ketone levels appear to be too small to draw conclusions regarding the effectiveness of administration of glucose, fructose, or no sugar.

In twenty-two patients the average twelvehour fluid intake was 4.496 L. and the average urine output 1.29 L., with an average retention of 3.13 L. or 69.6 per cent of the administered fluid. (Data from Figure 2.)

# COMMENTS

While the overall results showed no definite differences in fluid retention with different types of fluid (hypotonic, isotonic, hypertonic), a few patients did have diuresis with hypotonic fluids.

The fact that more water than electrolyte is \* Intake actually expressed as mM. P.

required is definitely shown by the fact that the hyperosmolarity of the serum which was present on entry in 52 per cent of the patients was still present after twelve hours of therapy in 46 per cent of the patients studied. This tendency to hyperosmolarity was increased by the use of hypertonic solutions, with the frequent occurrence of hypernatremia and hyperchloremia. An additional reason for the use of hypotonic solutions is the water requirement for the high solute load presented to the kidneys prior to and during the therapy of diabetic ketoacidosis. Butler [11] gives a figure of 3,500 mOsm. for urinary solute load in diabetic ketoacidosis. This would mean a water requirement of 2,500 cc. for urine water alone, at a specific gravity of 1.035 (1,400 mOsm./L.).

However, if shock or severe dehydration is present we believe that plasma and extracellular

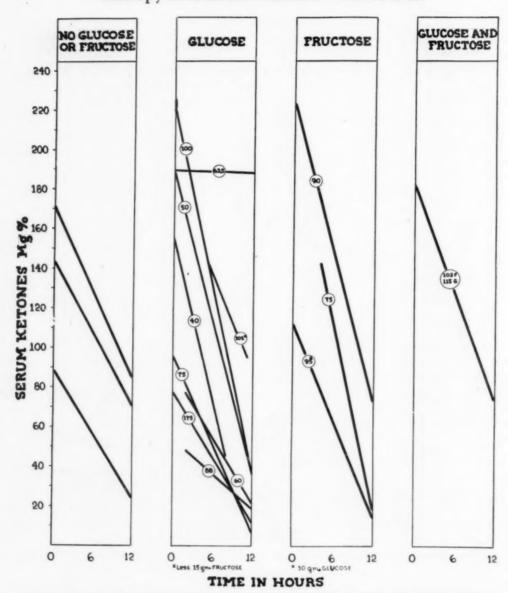


Fig. 4. Glucose and fructose therapy \* and serum ketone levels in diabetic ketoacidosis.

volume should be restored rapidly with isotonic fluids and, if indicated, dextran, plasma or whole blood (if anemia is present). This expansion of extracellular volume has priority over water requirement. Later, a hypotonic solution should be used to correct cell water deficits and provide water for the high urinary solute load, and to prevent occurrence of hyperosmolarity, hypernatremia and hyperchloremia.

There has been considerable discussion of the type of repair fluid for use in the correction of the acidosis of diabetic ketosis [11,12]. It has been postulated that with use of lactate or bicarbonate the serum bicarbonate can be raised

\* Number of grams of glucose or fructose administered indicated by circled figure.

rapidly at a time when the H<sub>2</sub>CO<sub>3</sub> concentration and pCO<sub>2</sub> are low due to hyperpnea, with production of a masked alkalosis. Also, it has been suggested that saline solution should be used for correction of both the extracellular fluid deficit and the acidosis [12].

As hyperpnea stops promptly within two to three hours of insulin and fluid therapy the problem of development of respiratory alkalosis rarely is a serious consideration. When simultaneous blood pH and serum bicarbonate level determinations were obtained (see Table IV as an example) the range of correspondence was good. We believe that sodium bicarbonate or ½6 molar sodium lactate is the treatment of choice for the acidosis, as there is a bicarbonate deficit which

should be corrected promptly; the acidosis may be increasingly detrimental, due to cellular and renal losses of electrolyte, particularly potassium [13]. While the normal kidney can compensate for a considerable acid load by bicarbonate and ammonia formation, this mechanism is strained to the maximum in diabetic ketoacidosis. Renal correction of acidosis becomes possible only as the ketone load decreases and this may require several hours of therapy. Also, the renal tubular mechanism that reabsorbs sodium and chloride in the ratio present in serum does not operate in the face of an acidosis to correct fully the imbalance of sodium and chloride in the glomerular filtrate which occurs when 0.9 per cent saline solution is used.

A mixture of ½ molar sodium lactate (or bicarbonate) and saline solution appears to us to give the best results for simultaneously correcting the acidosis and restoring the extracellular fluid volume, since this fluid contains not only sodium chloride but sodium bicarbonate.

If qualitative serum and urine acetone levels are obtained simultaneously with the serum bicarbonate determinations [14] there is little chance of overlooking serious ketosis, as suggested by Danowski [12], even though serum bicarbonate levels may have been raised to normal by bicarbonate or lactate administration.

Our results re-emphasize the point that the concentrations of electrolytes in serum do not necessarily reflect the total amount present in the body [8,12], as many normal or even elevated serum concentrations were found on entry at a time when there was a severe deficit of all electrolytes as shown by the balance studies.

In comparison to Danowski's results [12] in a large series of children with severe diabetic ketoacidosis, our patients had far more frequent low serum potassium and calcium levels, more high serum chloride levels, and fewer low sodium and phosphate levels on entry than his patients.

We believe that decrease in serum concentration of the extracellular ions (sodium and chloride) before therapy is due primarily to the hyperosmolarity of the extracellular fluid, because of the high blood sugar levels. High entry serum sodium and chloride levels are relatively uncommon and can only mean the urinary loss of more water than electrolyte. The occurrence of high serum chloride levels on entry without a corresponding increase in serum sodium concentrations may indicate a

shift of sodium into the cells for the partial replacement of potassium deficits. The occurrence of high serum sodium and chloride levels after therapy is usually due to a high intake of these ions, in addition to the use of hypertonic solutions, particularly of 0.9 per cent saline solution.

The entry serum concentrations of the primarily intracellular ions, potassium, magnesium and phosphate, may be low, high or normal. The factors responsible for these differences in serum levels are not entirely clear from our studies or those of others, but may include rate of tissue breakdown, steroid effects, state of renal function, effect of acidosis on movement of ions from intracellular to extracellular fluid, and competitive ion exchange in the kidney.

The problem of the range of deficits of fluid and electrolyte is complicated, as long-term studies (several days) are needed to define the magnitude of the deficits in intracellular ions. The replacement requirements, moreover, will vary from patient to patient.

Table vII gives the result of the balance studies in diabetic acidosis reported by others (nineteen patients) compared with ours (eight patients). Butler's [11] estimate of loss for severe dehydration (10 per cent of body weight) is also included in this table. Two groups determined [15,16] the retention of electrolytes during the early phase of treatment of diabetic ketoacidosis, and one or two days thereafter. One group (Nabarro et al. [17]) studied the retention of ions during the acute phase of insulin and fluid therapy, and for eight to twelve days thereafter. Two of the studies [18,19] were made during withdrawal of insulin for several days. Ours appears to be the only balance study in which all the intracellular ions (potassium, magnesium, phosphate) were given in the repair fluids during the early phase of treatment.

Butler [11] estimated a requirement of 5 to 12 mEq./Kg. of sodium for correction of 10 per cent dehydration. The sodium requirement in the balance studies in diabetic ketoacidosis showed a range of 5.1 mEq./Kg. to 13.3 mEq./Kg. Our figure of 7.0 mEq./Kg. corresponds with the figure of 7.2 mEq./Kg. from the long 8 plus day balance of Nabarro et al. The figure of Danowski and Darrow [15,16] of 10.4 to 13.3 mEq./Kg. appears high for the average, although not for the maximum requirement.

As to the requirement of chloride, the estimate of Butler [17] for 10 per cent dehydration was

TABLE VII

COMPARISON OF ESTIMATED FLUID AND ELECTROLYTE REQUIREMENT IN DIABETIC ACIDOSIS

Author	Type of Study	No. of Patients	Na (mEq./Kg.)	Cl (mEq./Kg.)	HCO <sub>4</sub> - (mEq./Kg.)	K (mEq./Kg.)	Mg (mEq./Kg.)	P (mM/Kg.)	H <sub>2</sub> O (L./Kg.
Martin et al. (this study)	Retention during 12 hours of therapy of diabetic acidosis*	8	7.0	4.0	4.7	2.7†	0.16†	1.0†	0.082-
Nabarro et al. [17]	Retention during therapy of diabetic acidosis and for 8 to 12 days after acute therapy on measured intake	7	7.2	5.1		5.0	0.56	0.5	0.087
Danowski et al. [15]	Retention during acute therapy of diabetic acidosis and up to 34 hours after acute therapy	8	10.4	9.5	***	6.0	****	****	******
Darrow [16]	Retention during acute therapy of diabetic acidosis and for 2 days after	1	13.3	9		6.1	-		0.114
Atchley et al. [18]	Loss during insulin	2	5.9	2.5		4.9	*****	****	0.089
Butler et al. [19]	Loss during insulin	1	5.1	4.0		5.6	0.8	1.3	
Butler*	Estimated loss 10 per cent dehydra- tion	Estimated	5–12	4.0		6.0	*****		0.06-0.1

\* Our figures might well be higher as we divided retention by 70 Kg. and this may not have represented average weight.

† This figure is too low for complete repair and only represents amount for acute therapy (see text).

4 mEq./Kg. The figures in the balance studies in diabetic ketoacidosis range from 2.5 to 9.5 mEq./Kg. Our figure was 4.0 mEq./Kg. The figures of Danowski and Darrow again appear high, 9.0 and 9.5 mEq./Kg. It is to be noted that in many of their patients marked hyperchloremia developed, as it did in the majority of our patients who received high chloride loads.

The problem of the requirement of the intracellular ions is complicated by the loss of nitrogen and the loss of electrolyte in excess of nitrogen. Butler [11] estimated the potassium loss in 10 per cent dehydration at 6 mEq./Kg. The range of requirement from the studies made in diabetic ketoacidosis is 5 to 6.1 mEq./Kg. The long-term study of Nabarro [17] gave a figure of 5 mEq./ Kg. Our figure of 2.7 mEq./Kg. is too low for several reasons: the short time period of the balance (twelve hours), in addition to the fact that 63 per cent of the serum potassium levels were low at twelve hours in our series. For the first period of correction, however, when confronted with the problem of giving potassium in the face of dehydration, and low urine volume, we believe that this amount is adequate for prevention of most acute extracellular deficits and for partial replacement of cellular stores.

Complete correction will require several days and will occur from dietary intake, as shown in the study of Nabarro et al. [17].

While we do consider that it is undoubtedly hazardous to administer potassium early, in the face of elevated serum potassium levels or poor renal function, it may be equally hazardous to delay the early administration of potassium in patients with serum levels under 4 mEq./L. For this reason we believe that it is essential to determine the serum potassium level on entry, since 15 per cent to 18 per cent of the patients will then have a level below normal.

As far as phosphate therapy is concerned, there is no unanimity of opinion as to whether or not it should be used, although all agree that there is a marked fall in the serum phosphate level during intensive fluid and insulin administration. Guest [20] and Franks et al. [21] noted some improvement in the state of consciousness with administration of phosphate. We noted no change in the clinical state of our patients who were treated with phosphate.

Only a few authors have studied the phosphate balance. (Table VIII.) The urinary loss per twenty-four hours in the three patients in whom insulin was withdrawn ranged from 24 to 53 mM. phosphorus. One patient who was given

TABLE VIII
PHOSPHORUS THERAPY IN DIABETIC ACIDOSIS\*

Group	Type of Study	Time Period (days)	No. of Patients	P Intake (average 24 hr.)	P Intake (range, mM)	Urine Output (average, mM/24 hr.)	Urine Output (range, mM/24 hr.)	% Intake Retained (average)	% Intake Retained (range)	Estimated Require- ment (mM/Kg.)
Martin et al. (this study)	Retention during acute treatment of diabetic ketoacidosis	0.5	8	44	11-86	15	3–59	72	29-95	1.0
Franks et al. [27]	Retention during acute treatment of diabetic ketoacidosis	1	10	64	42-80	25	13–46	61	44-85	0.9
Atchley et al. [18]	Insulin withdrawal	8	2	37.5	33.8-41.2	38.5†	52.7-24.3		0 to +41	
Butler et al. [19]	Insulin withdrawal	3.4	1	0		28.5‡	*******		******	1.3
Nabarro et al. [17]	Retention during acute treatment of diabetic acidosis	1	7	8	0-12	35	14–67			*****
	Retention after acute treatment	8-12	**				*******	Mean retention 37 mM. P		0.5
Darrow et al. [16]	Retention during acute treatment of diabetic acidosis	24	1	0	*******	7.5	******			
* * * * * * * * * * * * *	Retention after acute treatment	2	**	****	******			Retention 148.5 mM. P§		5.6

\* Figures from other authors converted to mM. P for comparison with our studies.

† Last day of insulin withdrawal.

Urinary P for 3.4 day period equals 94.8 mM.; this gives 28.5 mM./24 hr.

Patient on a very high P intake from milk diet; stools not analyzed.

no phosphate while receiving the acute therapy of diabetic acidosis had a twenty-four-hour urinary loss of 7.5 mM P. The seven patients of Nabarro [17] who were given no phosphate or small amounts (0 to 12 mM P) during the acute phase of therapy had a twenty-four-hour urinary loss of 14 to 67 mM P; average 35 mM. P. In our series, patient B. V. O. who received no phosphate had a urinary output of 10.42 mM. P in six hours. In the only other study besides ours in which phosphate was given in large amounts (Franks et al. [21]) 42 to 89 mM P (average 64 mM) was given in twentyfour hours, with a urinary output of 13 to 46 mM P and retention of 44 to 85 per cent of the amount given. This would indicate a requirement of 0.9 mM P/Kg. However, the serum phosphate levels were not maintained in this series after infusion was stopped. In Nabarro's [17] long-term balance study there was a mean retention for the eight- to twelve day period of 37 mM P, or a requirement of 0.5 mM/Kg. Our patients (Table v) had an average retention of 72 per cent of the administered phosphate (11 to 86 mM. P administered), with urinary

loss during twelve hours ranging from 3 to 59 mM P. This gives an estimated requirement of 1 mM P/Kg.

We noted no complications, such as the development of tetany, in giving phosphates but believe that if administered early (zero to two hours) when the serum level may be high there will be increased renal clearance and loss of a large amount of the administered phosphorus in the urine. (Table IV.) The fall in serum phosphate level with insulin therapy appears to be due to the shift of a large amount of phosphorus into the cells, and some urinary loss in addition. (Tables IV and VI.)

As to magnesium, Butler [19] estimated a requirement of 56 mEq. or 0.8 mEq./Kg. in one patient, during 3.4 days of insulin withdrawal and an additional day of vomiting and thirsting. Nabarro [17] in his long balance study reported a mean retention from the diet of 39 mEq. magnesium, or 0.56 mEq./Kg. assuming 70 Kg. per patient. The serum magnesium levels did not fall below the normal range in the four patients in our series given 6 mEq. of magnesium or more. (Table v.) We conclude, therefore, that

in the early phase of therapy 0.2 mEq./Kg. would be sufficient.

These studies show, as do previous reports from our laboratory [22], that the serum magnesium falls because of urinary loss and a shift into the cells. In patients B. V. O. and E. M. (Table v) the fall in serum magnesium was due primarily to an intracellular shift, as the urinary loss was small (2 and 1 mEq. respectively). In patient R. W. (Table v) the urinary loss alone (3.5 mEq.) could explain the fall in serum concentration.

As shown in Table vII there was good correspondence in all the studies in respect to water requirement, .06 to 0.114 L/Kg.

As a result of this study, and the results recorded by others, we use the following solutions in sequence in the treatment of diabetic acidosis and ketosis: 2 to 3 L. of a combination of <sup>3</sup>/<sub>4</sub> L. <sup>1</sup>/<sub>6</sub> molar sodium lactate and <sup>1</sup>/<sub>4</sub> L. 0.9 per cent saline solution, followed by 3 to 4 L. of modified Butler's solution. Unless there is a high serum potassium level or severe oliguria, potassium chloride (1 to 2 gm.) is added to the second liter of intravenous fluid, and 1 ampoule of special potassium phosphate solution is added to the third, fourth and fifth liters of intravenous fluid. More potassium is administered if there is evidence of a serious deficit.

Shock, while not discussed specifically in this paper, is treated vigorously with dextran, plasma or whole blood (if anemia is present) and vaso-pressors (levophed®).

# SUMMARY

A detailed summary is given of the fluid and electrolyte therapy used in the early phases of treatment of twenty-nine episodes of severe diabetic ketoacidosis.

There was little difference in the volume of fluid retained when repair solutions of varying tonicity were employed. Hyperosmolarity of the serum was present in 52 per cent of the patients on entry and in 46 per cent of the patients after twelve hours of therapy. When hypertonic fluids were used there was more hyperosmolarity of the serum after twelve hours of therapy than with hypotonic fluids, and hypernatremia and hyperchloremia were frequently noted. This indicates the need for use chiefly of hypotonic fluids.

Factors influencing the correction of acidosis included the lactate/chloride ratio of the intravenous fluids used (considered to be best at a ratio over 1.0), the entry serum chloride level,

the use of hypertonic solutions, large loads of 0.9 per cent sodium chloride and the rate of fall of the blood ketone levels.

Detailed balance studies in eight patients correlated well with previous estimates of 5 to 10 per cent body fluid loss and with balances of certain ions.

From these studies we believe that the average range of intake in the early, more acute phases of treatment should be 70 to 120 ml.  $H_2O/Kg.$ ; 7 to 10 mEq. Na/Kg.; 5 mEq. Cl/Kg.; 2 to 3 mEq. K/Kg.; 0.2 mEq. Mg/Kg.; 1 mM P/Kg.; and 4 to 5 mEq. HC $\bar{O}_3/Kg$ .

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# Progression of Amaurotic Family Idiocy As Reflected by Serum and Cerebrospinal Fluid Changes\*

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NEANTILE amaurotic family idiocy (Tay-Sachs disease) has been classically considered a degenerative disease restricted to the neurectodermal elements of the body [1,2]. The ubiquitous involvement of ganglion cells in this disorder is in striking contrast to the normal morphology of other somatic tissues [3]. This histologic characteristic (i.e., circumscribed implication of ganglion cells to the exclusion of all other cell types), in association with certain clinical features (i.e., onset within the first year of life, macular involvement, heredofamilial tendency), forms the acknowledged definition of the disease. These characteristics, in addition, partially serve to distinguish amaurotic family idiocy (AFI) from other varieties of lipoidosis [4].

If the accumulated pathologic observations indicating a localization confined to ganglionic tissue are accepted, a diagnostically serologic reflection of this degenerative disorder would probably not be anticipated. Repeated observations of the lipid constituents of blood, in fact, have consistently failed to disclose any abnormalities [5]. In a related disorder, Niemann-Pick's disease, the dystrophic intracellular storage phenomenon is demonstrable in reticuloendothelial cells throughout the body (in addition to the ganglionic disorder), and chemical analysis of serum repeatedly showed an elevation of total lipids and a depression of serum phospholipids [4,6]. It must be borne in mind, however, that the previous efforts directed toward establishing some consistent serum abnormality in AFI have been confined to the lipid components and inorganic elements of blood.

The absence of any demonstrable change in these serum substances, therefore, has been implicity incorporated into a broader characterization of AFI.

During the course of a comprehensive survey of fifty-five cases of AFI concerned principally with morphologic and genetic aspects [7,8], a wide range of biochemical tests were made in the blood and cerebrospinal fluid derived from the nineteen most recent cases in this series. It should be emphasized, however, that this was not a random application of tests but rather a choice of procedures based upon known or postulated characteristics of this particular disorder. Particular efforts were made to evaluate the blood levels of a number of enzymes, protein fractions and protein-linked substances.

The present report is concerned with a summation of these biochemical studies and the possible relationship of the attendant abnormalities to the evolution of the disease.

## SELECTION OF PATIENTS

Nineteen consecutive patients with AFI were studied by the laboratory procedures to be outlined. In many instances the tests were performed serially at monthly intervals for periods ranging up to two and one-half years. In addition, one case of Niemann-Pick's disease as well as one case of diffuse sclerosis were included in the studies for purposes of comparing other neurologic disturbances of similar pathophysiologic dimensions. The control results were based upon equivalent studies performed upon children of comparable age suffering from a wide range of unrelated neurologic disorders includ-

<sup>\*</sup> From the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, New York. This work was carried out under the auspices of The National Tay-Sachs Association.

ing meningocele, convalescent poliomyelitis, hydrocephalus, infantile epilepsy and numerous other disorders.

The children comprising this study were often hospitalized shortly after establishment of the diagnosis and remained under clinical observation until death ensued. Autopsies were performed on almost all the patients succumbing from AFI. The clinical diagnosis, in these nineteen cases, was based upon the collective presentation of apathy, progressing weakness, developing amaurosis, arrested development, the emergence of abnormal movements, hypersensitivity to sound, and macular degeneration. The children were all of Jewish extraction. The pertinent clinical data concerning these nineteen cases are outlined in Table 1.

In addition to the classically described morphologic alterations assigned to this disorder, a number of pathologic changes which were constantly seen were observed, which permitted a rational evolutionary subdivision of the disease [7]. Rather than assigning a constant pathologic picture to the disease it was found more appropriate to consider the disorder in three phases, each with a typical neuropathologic substrate (to be outlined). Phase I was designated as that span beginning with the initiation of symptoms (generally about the fifth month of life) to the fourteenth month of recognized illness. Phase II included the span between the fifteenth month of illness to the twenty-fourth month. Phase III covered the clinical aspects beyond twenty-four months of clinically determined disease. Although these chronologic subdivisions were initially based upon pathologic criteria, the classification in subsequent studies was shown to be a point of considerable convenience when applied to the clinical and radiographic aspects of the disease [8].

## CRITERIA AND CHARACTERISTICS OF DISEASE PHASES

Phase I (Zero to Fourteen Months of Illness). In many cases it was difficult to establish precisely the clinical onset of the disorder. Often there were vague prodromas which, while not intimately associated with AFI, may have represented the clinical beginning of the disease. In all cases, however, the first unqualified clinical abnormality (e.g., failure to recognize formerly familiar objects, loss of ability to perform certain motor acts, etc.) was accepted as

the commencement of AFI. In the subsequent six months the fully established clinical picture emerged completely. Blindness was uniformly found (in association with retinal cherry-red spots) as well as progressive weakness and evidence of further neurologic incapacity. The

Table 1

Data on nineteen patients with amaurotic family idiocy, one patient with niemann-pick's disease and one patient with diffuse sclerosis

Case No.	Sex	Age at Onset of Symp- toms (mo.)	Clinical Dura- tion (mo.)	Observation (mo.)	Autopsy	Diagnosis
5*	М	6	25	20	Yes	AFI‡
6	F	7	28	18	Yes	AFI
7	F	4	33	14	Yes	AFI
8	M	5	42	9	Yes	AFI
9	F	5	17	10	Yes	AFI
10	F	6	30	21	Yes	AFI
11	F	7	31†	28†	Alive	AFI
12	F	6	24	20	Yes	AFI
13	M	9	21	8	No	AFI
14	F	9	18†	17†	Alive	AFI
15	M	8	25	12	Yes	AFI
16	F	7	9	2	No	AFI
17	F	4	12†	14†	Alive	AFI
18	M	8	18†	9†	Alive	AFI
19	F	4	9	5	Yes	AFI
20	F	7	18†	16†	Alive	AFI
21	M	4	44	6	Yes	AFI
22	M	5	14†	7†	Alive	AFI
55	M	6	10†	6†	Alive	AFI
50	M	5	10†	7†	Alive	Niemann-Pick's Disease
65	F	75	44†	41†	Alive	Diffuse sclerosis

\*Figures indicate series numbers used during overall studies on AFI. †Figures as of May, 1957.

Amaurotic family idiocy

afflicted child showed little spontaneous movement except during convulsive seizures. No demonstrable muscle atrophy was observed. Nutrition was generally adequate although gavage was occasionally necessary. There was obvious retardation of growth. Weekly occipitomental and chest circumstances as well as body weights were recorded in all cases. There was a retardation of these parameters when compared with normal data. Pneumoencephalograms were performed at frequent intervals and showed mild dilatation of the lateral ventricles with radiographic evidence of cerebral atrophy as exemplified by focally increased amounts of air in the supratentorial subarachnoid space. Ventricular dilatation was also observed in the third and fourth ventricles. The basilar cisterns were unusually widened.

In most children succumbing within fourteen



Fig. 1. Coronal section of brain (Case 8) showing massive central demyelination and cystic degeneration of bilateral parietal white matter.

months of the onset of disease, the necropsy findings were characteristic. The brain was diffusely atrophic and weighed less than normal. The cerebral gyri were narrowed and the sulci widened. The atrophy was also visibly apparent in the infratentorial structures. Histologic sections disclosed typically ballooned neurons distended with a poorly staining granular substance. The cytoplasmic chromatin bodies were diminished. All levels of the neuraxis showed some degree of typical histologic change in addition to a mild reactive gliosis. Cell loss, as distinguished from cell involvement, was relatively minimal in most segments of the nervous system. A slight but diffuse demyelination was also noted throughout.

Phase II (Fifteen to Twenty-four Months of Illness). Recorded clinical observations during this aspect of the disorder showed only a quantitative increase of many of the characteristic symptoms of Phase 1. Generally the afflicted child became increasingly hypotonic and lapsed into a vegetative existence. Some displayed episodes of convulsive seizure, occasionally followed by brief periods of decerebrate rigidity. The characteristic opisthotonus rarely lasted more than a few moments. Hyperacusis was still a prominent feature. Tendon reflexes were diminished but demonstrable and pupils still sluggishly responded to light stimulation. A mild muscle atrophy became evident. The cephalometric observations now showed a surprising reversal. About eighteen to twenty-one months after the onset of pertinent symptoms the head circum-

ference measurements inordinantly increased to about 20 per cent above normal. Simultaneous observations of chest circumference, height and weight, however, showed no equivalent change but rather a continuing retardation in accordance with the previous patterns noted in Phase 1. Pneumoencephalograms also showed a reversal of the findings characteristic of Phase 1. The previously demonstrable supratentorial ventricular dilatation was now less pronounced or absent and the cerebral mantle atrophy was no longer visualized. In contrast, however, the roentgenographically demonstrable cerebellar and brain stem atrophy persisted. Autopsies performed during Phase II corroborated the reversal in the pattern of cerebral atrophy exemplary of Phase 1. Brain weights were within normal limits or in some instances greater than normal. In most cases the brain was of essentially normal contour and proportion. The ventricles were no longer dilated. A disproportionate atrophy of the cerebellum and brain stem was now seen. Histologic studies of the neuraxis showed a widespread storage disorder of the ganglion cells, similar to that seen in Phase I. In addition, numerous cells, particularly those of the cerebral gray matter, had disappeared and a vicarious gliosis was now evident. A more widespread demyelination was observed in the subjacent white matter of the cerebral hemispheres with a moderate degree of astrocytic and microglial response.

Phase III (More than Twenty-four Months of Clinical Illness). Clinical observations of this period recorded a continuation of those aspects previously noted. The afflicted child was totally immobile and prone to recurrent pneumonic infection. Careful nursing management was required to prolong existence. Muscle atrophy of all limbs coexistent with a total hypotonicity was characteristic. Tendon areflexia and a general lack of responsiveness to any form of visual or tactile stimulation was present. Progressive megalencephaly, first noted toward the latter aspects of Phase II, became more noticeable and was even more conspicuous when compared with retarded development of the other somatic parameters. Chest circumference ceased to increase and not infrequently diminished in the ensuing months. Body weight often remained stationary as inanition progressed. Serial pneumoencephalography confirmed the fact that the head enlargement was not the consequence of hydrocephalic dilatation but rather the result of

an actual expansion of cerebral tissue volume. The bulk of brain tissue was significantly increased as determined by the width of radioopacity between the compressed lateral ventricular borders and the calvarium. In contrast, the infratentorial atrophy persisted through Phase III and the increased amount of air in the basilar cisterns continued. The augmented cerebral volume resulted in widely separated fontanelles. Autopsies performed during this period of the disease disclosed an unusual degree of cerebral enlargement. Brain weights were considerably above normal, in one instance as much as 1,800 gm. (normal 980 gm.). The external appearance of the intracranial contents was characteristic. The cerebral hemispheres were markedly increased in volume and the surface convolutions were broadened and flattened, giving the appearance of a significant expansion of the mantle tissues. On the other hand, the infratentorial structures (cerebellum and brain stem) were markedly atrophic and often appeared to be mere appendages of the huge cerebral hemispheres. Consecutive cross sections of the incremented cerebrum showed widespread demyelination of the deeper cerebral white matter, with focal areas of cystic degeneration, edema and gliosis. (Fig. 1.) Histologic preparations confirmed the continuation of the dystrophic storage process and in addition showed widespread disintegration of the afflicted neurons. The white matter was the site of intensive demyelination. The apparently contradictory phenomenon of late megalencephaly in the presence of a progressive disease characterized by neuronal degeneration was clarified by the demonstration of an unusually reactive glial over-compensation and hyperplasia within the cerebral white matter, believed to be stimulated by the liberation of abnormal lipoid substances from the lysed neurons.

#### METHODS

Serum aldolase determinations were performed by the method of Sibley and Lehninger [9] and serum glutamic-oxalacetic acid transaminase (GO-T) by the procedure of Karmen, Wroblewski and La Due [10]. Determination of GO-T in the cerebrospinal fluid was carried out by essentially similar technics with slight modification because of the dilution of the enzyme [11]. The technic employed for moving boundary electrophoresis of serum proteins has been described in previous publications from this

laboratory [12,13]. Total proteins were determined by a biuret procedure [14] using standards checked with the micro-Kjeldahl method. The neuraminic acid content of serum and its albumin/globulin distribution were analyzed by the recently developed procedure of Saifer and Gerstenfeld [15] which is based on the diphenylamine reaction [16].

#### RESULTS

Serum Aldolase. One hundred and twelve separate determinations were performed in fourteen patients with AFI. (Table II.) In most instances the tests were performed at monthly intervals. During the first phase of the disease the serum level of this enzyme was within normal limits  $(7.14 \pm 0.73 \text{ units/cc.})$  or only minimally elevated, averaging 10.34 units/cc. Commencing approximately in the ninth month of determined illness, the serum aldolase levels became significantly increased, reaching a high point approximately in the fifteenth month of disease. (Figs. 2 and 4.) In only one child did the serum aldolase fail to rise above 10 units/cc. during Phase II of the illness. In those children surviving beyond the sixteenth month of determined sickness the serum enzyme levels almost invariably fell to the normal range, usually by the twenty-first month of illness. In one child there was a second rise of the serum aldolase coincident with terminal infection. A roughly comparable curve was noted in the results of one case of Niemann-Pick's disease studied serially, the high point however being of greater magnitude than in AFI. (Fig. 5.) Monthly aldolase determination in one case of diffuse sclerosis (Fig. 6) showed no significant or prolonged elevations of the serum level of this enzyme. (Table III.)

Serum GO-Transaminase. Ninety-two separate determinations of this enzyme were performed in the serum of thirteen patients with AFI, generally at monthly intervals. (Fig. 3.) During Phase I of the disease there was a marked elevation, averaging 113.8 units/cc. (normal 22.1 ± 6.7 units/cc.). In the succeeding months of the disease a wide fluctuation was noted, but in all instances the values were well above the upper limits of normal. When the results were cumulatively studied a slow regression of the marked hypertransaminasemia characteristic of Phase I was noted. During Phase III of the illness an average level of 82.6 units/cc. was recorded. The individual findings in one typical

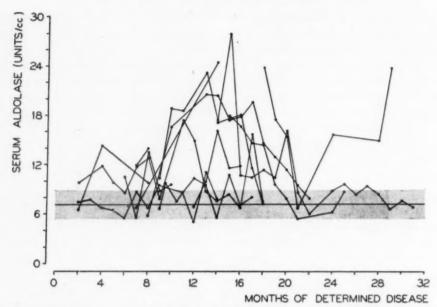


Fig. 2. Serial serum aldolase levels of fourteen patients with AFI. The shaded area represents the normal range.

case of AFI for both aldolase and SGO-transaminase are shown in Figure 4. There is no apparent parallelism between the two enzymes. A marked elevation of serum GO-T was also seen in the case of Niemann-Pick's disease studied. (Fig. 5.) In one determination a level of 600 units/cc. was noted. The serum GO-T levels in a case of diffuse sclerosis were normal for the

majority of the clinical course (Fig. 6) except for a mild elevation during a period of four months coinciding with a sustained hip fracture.

Serum Protein Electrophoresis. The accumulated results are shown in Tables II and III. Thirty-three electrophoretic patterns were examined in nineteen cases of AFI. A mild depression of the total protein was evident, generally becoming

TABLE II
COMPILATION OF BIOCHEMICAL DATA IN RELATION TO PHASE OF AMAUROTIC FAMILY IDIOCY

Test	No. of Patients	Total No. of Determi- nations	Phase 1	Phase II	Phase III	Normal
Serum aldolase (units/cc.)	14	112	10.34±0.60*	13.02+0.74	10.48 + 1.37	7.14+0.73
Serum GO-transaminase (units/cc.)	13	92	113.8 ±4.6	93.8 ±4.2	82.6 ±4.4	22.1 ±6.7
Serum protein (gm. %):						
Total proteins	19	33	6.94±0.07	6.63±0.15	6.33†	$7.35 \pm 0.06$
Albumin	19	33	3.75±0.08	3.70±0.13		4.23 ±0.08
Alpha-1 globulin	19	33	$0.51 \pm 0.02$	$0.50 \pm 0.02$	0.35	0.47±0.02
Alpha-2 globulin		33	0.96±0.05	$1.00 \pm 0.06$	0.80	$0.65 \pm 0.02$
Beta globulin		33	1.05 ±0.03	$0.85 \pm 0.03$	0.87	$1.00 \pm 0.03$
Gamma globulin	19	33	0.65±0.06	$0.56 \pm 0.04$	0.80	0.99±0.04
Serum neuraminic acid:						
Total serum neuraminic acid						
(mg. %)	14	49	88.8 ±3.3	87.0 ±2.8	83.4 ±3.0	77.4 ±1.2
Globulin neuraminic acid (%)						
Total neuraminic acid	14	49	61.3 ±3.9	63.6 ±1.3	62.9 ±2.6	54.7 ±0.71
Globulin neuraminic acid (%)						
Globulin	14	49	1.94±0.13	1.82±0.06	$1.92 \pm 0.12$	1.46±0.03

\* Mean ± Standard Error (S.E.).

† No S.E. determined since the number of tests were less than 7.

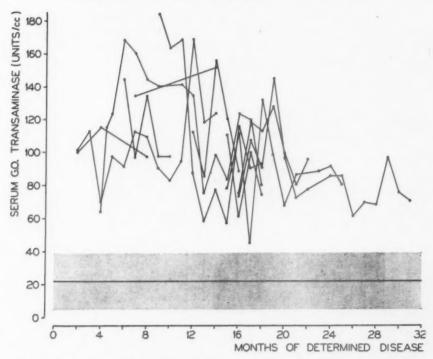


Fig. 3. Serial serum GO-transaminase levels of thirteen patients with AFI.

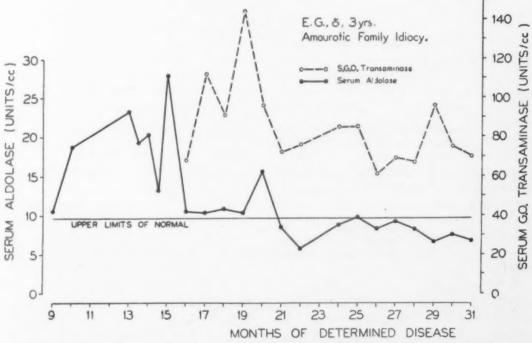


Fig. 4. Comparison of serial serum aldolase and serum GO-transaminase levels in a patient with AFI.

more pronounced as the disease proceeded. There was no significant variation in the determined data from phase to phase, however. The alpha-1 globulins were within normal limits but the alpha-2 globulin fractions were almost invariably elevated to a significant degree. The beta globulins were mildly depressed in the

latter phase of the disease. The gamma globulin component of serum protein was uniformly depressed throughout the entire course of the illness. A single serum protein electrophoresis from the case of Niemann-Pick's disease disclosed moderate elevations of the alpha-1, alpha-2 and beta globulin fractions but no

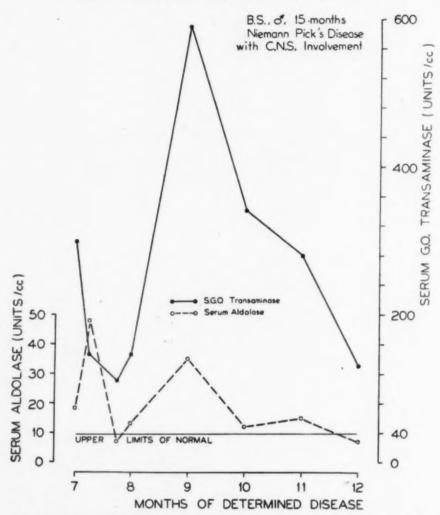


Fig. 5. Comparison of serial serum aldolase and serum GO-transaminase levels in a patient with Niemann-Pick's disease.

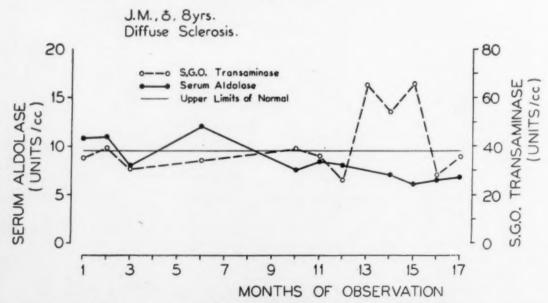


Fig. 6. Comparison of serial serum aldolase and serum GO-transaminase levels in a patient with diffuse sclerosis.

TABLE III
BIOCHEMICAL FINDINGS IN CASE OF NIEMANN-PICK'S DISEASE AND CASE OF DIFFUSE SCLEROSIS

	Niemann-Pick's Disease		Diffuse Sclerosis		
Test	No. of Deter- minations	Findings	No. of Deter- minations	Findings	Normal
Serum aldolase (units/cc.)	8	19.65 ± 5.1*	13	8.25±0.57	7.14±0.73
Serum GO-transaminase (units/cc.)	8	265.9 ±61.3	13	40.4 ±4.4	22.1 ±6.7
Serum Protein (gm. %):					
Total proteins	1	7.02†	1	8.46	$7.35 \pm 0.06$
Albumin	1	3.05	1	4.33	$4.23 \pm 0.08$
Alpha-1 globulin	1	0.65	1	0.42	$0.47 \pm 0.02$
Alpha-2 globulin	1	0.83	1	0.97	$0.65 \pm 0.02$
Beta globulin		1.65	1	1.53	$1.00 \pm 0.03$
Gamma globulin		0.84	1	1.20	0.99 ±0.04
Serum Neuraminic Acid:					
Total serum neuraminic acid (mg. %)	2	69.5	12	89.9 ±2.9	77.4 ±1.2
Globulin neuraminic acid (%)	,				
Total neuraminic acid	2	54.5	12	67.1 ±1.3	54.7 ±0.71
Globulin neuraminic acid (%)					
Globulin	2	2.37	12	$1.72 \pm 0.06$	1.46 ±0.03

\* Mean ± Standard Error (S.E.).

† No S.E. determined since the number of tests were less than 7.

disturbance of the gamma globulin content. The alpha-2 and beta globulin components in the patient with diffuse sclerosis were also elevated, the gamma globulin being normal.

Serum Neuraminic Acid. Forty-nine determinations of serum neuraminic acid, as well as the albumin and globulin distribution of this substance, were obtained in seventeen patients with AFI. The total serum neuraminic acid was elevated to an average range of 83.4 to 88.8 mg. per cent and showed no significant variation during the evolution of the disease (normal, 77.4 mg. per cent). A ratio of globulin neuraminic acid/total neuraminic acid (GN/TN) showed a more constant deviation from normal, averaging approximately 61.3 to 63.6 per cent for the cases of AFI as contrasted to 54.7 per cent for normal subjects of this age. Still another ratio formed by globulin neuraminic acid/globulin proteins (GN/GP) was also significantly different in the cases of AFI, averaging 1.82 to 1.94 as contrasted to 1.46 per cent in cases of normal individuals. Only two serum neuraminic acid determinations were performed in the case of Niemann-Pick's disease. The total neuraminic acid averaged 68.3 mg., per cent. The GN/TN ratio was also within normal limits but in one determination,

the GN/GP ratio was markedly elevated while the other was normal. (Table III.)

Cerebrospinal Fluid GO-T Levels. The GO-transaminase levels in fifteen children with neurologic disorders (e.g., meningomyelocele, epilepsy, cerebral palsy, etc.) averaged 13.3 units/cc. In contrast, six children with AFI who were submitted to the same procedure gave an average of 44.0 units/cc. The cerebrospinal fluid GO-T in the one case of Niemann-Pick's disease was also markedly elevated (41 units/cc.) but in the case of diffuse sclerosis it was below normal limits (8 units/cc.).

### COMMENTS

The selective ganglionic disturbance typifying AFI has been repeatedly substantiated by histologic technics in the seven decades since Sachs' original pathologic description of the disorder [1]. Literally scores of publications have commented briefly upon the normal structure of somatic tissues and the lack of any attendant clinical evidence indicating an underlying or independent non-neurologic disorder. With considerable justification, therefore, the concept of selective affection of certain ectodermal elements has arisen and the illness has sometimes been

designated a "blastomeric disease" [2]. The very lack of extracerebral abnormality is presently accepted as a necessary component feature of the diagnosis. But while the fundamental disease process may conditionally be conceived of as structurally restricted to ganglionic elements, secondary consequences stemming from such a cellular disorder may be

In accordance with other heredodegenerative diseases of the central nervous system, AFI shows some segmental selectivity within the nervous tissues [2]. Thus, while all neurons are implicated to some measure, those cells subserving a motor function are affected to a greater degree. Histologic preparations of spinal cord cross sections, for example, show more pronounced degeneration of the anterior horn cells than of the other (lateral or posterior) nuclear groups. Similarly, motor cranial nerve nuclei are more severely implicated than the sensory nuclei [7]. The diffuse lower motor neuron involvement is initially appreciated as paresis, and ultimately as paralysis and muscle atrophy; expressed metabolically, as the heightened liberation into the blood stream of many of the intracellular enzymes contained within skeletal muscle. It has been shown clinically and experimentally that neuromuscular disability, particularly when consequent to progressive involvement of anterior horn cells (e.g., progressive spinal atrophy, amyotonia congenita), is associated with serum elevation of the enzyme fructoaldolase [17,18]. In contrast, muscle atrophy caused by disuse or inanition, such as would be anticipated in severe neurologic disease without ganglionic involvement (e.g., diffuse sclerosis), is not associated with any consistent deviation of the serum aldolase. In thirteen of the fourteen patients with AFI examined serially by this procedure, a significant elevation was demonstrable. When there was opportunity for aldolase determinations from the commencement of the disease to its termination, a typical pattern became evident. During the initial months of the disease, the serum aldolase levels were normal. Toward the end of Phase 1 of the illness the serum aldolase was elevated, generally to levels of about 15 units/cc. The elevation generally persisted for periods of three to twelve months and almost invariably reverted to normal levels during Phase III of the disease. The hyperaldolasemia coincided with the clinical appearance of skeletal muscle atrophy.

The aldolase curves from cases of AFI were graphically similar to those obtained in experimental animals in which a major motor nerve was severed (i.e., a delayed elevation and eventual reversion to normal values) [17]. In one case of Niemann-Pick's disease studied the aldolase was also significantly above normal. In other infantile non-ganglionic neurologic disorders. including one case of far-advanced diffuse sclerosis, the serum aldolase remained normal

despite evident muscular atrophy.

Serum GO-T, an enzyme related to the intracellular synthesis of glutamic and oxalacetic acids, is widely distributed in tissues and particularly in cardiac musculature. Tissue damage. including myocardial necrosis secondary to coronary artery occlusion, therefore results in liberation of this enzyme into serum with subsequent hypertransaminasemia. Hepatic tissues are similarly characterized by significant concentrations of GO-T, hence hepatic necrosis is reflected by a serum increase of the enzyme [19]. Three points stand out concerning the relationship of elevated serum GO-T and tissue necrosis: (a) The tissue undergoing necrosis must contain a high enzymatic content (e.g., myocardium, liver) to permit a measurable release of the GO-T into the serum. (b) A hypertransaminasemia without further biochemical or clinical information can therefore only be construed as a non-specific indicator of tissue degeneration. (c) Serum elevation of GO-T is approximately proportional to the duration of active necrosis of the appropriate tissues. Thus, for example, the enzyme elevation following myocardial infarction may persist for only three to eight days and then revert to normal, indicating that the affected tissues have been exhausted of enzymatic content. A subsequent rise in the absence of other pathologic changes would therefore point to a new myocardial insult or further topographic progression of the first lesion.

The hypertransaminasemia associated with all the cases of AFI presently reported may be interpreted, therefore, as indicating active necrosis of neural tissues, since no myocardial or hepatic degeneration is evident. To reinforce this contention, the normal brain has been shown to contain a high concentration of the enzyme. In all previously recorded examples of elevated serum GO-T, however, there was an impermanent elevation. The prolonged hypertransaminasemia in AFI would indicate con-

tinuing tissue degradation, in accordance with the progressive nature of the disease. While hypertransaminasemia is by no means pathognomonic of any tissue localization or diagnosis. its occurrence should be accorded a different interpretation when seen in an infant. An elevation persisting for months in a baby would also be suggestive of a disease characterized by continuing tissue degeneration, and in the absence of hepatic dysfunction, likely to be of cerebral origin. Application of this procedure to a wide range of other pediatric neurologic diseases has uniformly failed to disclose any instance of prolonged hypertransaminasemia. A protracted elevation of serum GO-T in an infant, therefore, can probably be equated with the diagnosis of AFI or Niemann-Pick's disease, a related disorder.

Since both muscle and brain contain the enzymes aldolase and GO-T, it might seem arbitrary to attribute the hyperaldolasemia to neuromuscular atrophy and the hypertransaminasemia to cerebral necrosis. The aldolase level of brain tissue is far lower than in striated musculature [20], hence the quantitative aldolase liberation resulting from degeneration of the former tissues would be relatively inappreciable. The normal serum aldolase values of Phase III of AFI, a period of extensive grey matter degeneration, offers additional indication that brain damage alone does not result in a hyperaldolasemia. Further, the normal aldolase levels in the early aspects of Phase 1 of the disease, the elevation extending through Phase II, and the depression to normal levels in Phase III are in approximate correlation with the development of secondary muscular atrophy. The serum GO-T is constantly elevated through all phases of the disorder, showing a slightly greater elevation in Phase 1, and bears no correspondence to the attendant muscular atrophy. In contrast to aldolase which sensitively responds to myelopathic muscle atrophy, serum GO-T has been shown to be normal in cases of muscular atrophy caused by anterior horn cell disease.

The marked elevation of GO-T in the cerebrospinal fluid noted in six cases of AFI also would indicate that continuing intracranial tissue degeneration is the source of the liberated enzyme. Wakim and Fleisher [21], and Green and his associates [22] have shown that spinal fluid GO-T is increased in instances of experimental or clinical cerebral infarction. Their data further show that the magnitude of eleva-

tion is essentially proportional to the size of the infarct. Green and his co-workers also demonstrated that markedly elevated serum GO-T (e.g., cases of chronic hepatic disease) was not reflected in spinal fluid, possibly the result of a relative impermeability of the blood-brain barrier. Conversely, however, a modest serum GO-T elevation was seen in some instances of cerebral necrosis. Thus, while the blood-brain barrier is operative in both directions, the permeability is probably greater centrifugally. The results in AFI would strengthen this contention.

The lack of any sustained hypertransaminasemia in the one case of diffuse sclerosis observed may indicate that the GO-T localization within nervous system tissue is predominently in gray matter, a region immune to the degenerative changes characteristic of this disorder.

Quantitative electrophoretic data of the serum protein fractions were obtained in nineteen cases of AFI [23]. No statistically significant alterations were apparent in the total protein or albumin and globulin fractions. However, an elevation of the alpha-2 globulin fraction was seen, with diminished values of gamma globulin. These changes were generally evident in all stages of the disease, perhaps increasing somewhat with duration, but no correspondence between structural alterations and deviations in protein fraction content of the serum was obvious. Studies reported elsewhere have also indicated a depression of the gamma globulin content of cerebrospinal fluid in AFI [23]. No explanation for these changes is available but the consistency of these findings, with particular reference to the hypogammaglobulinemia, may suggest that AFI may well extend beyond the confines of nervous system tissue even though no extraneural structural changes are evident by histologic technics presently available. Preliminary studies in progress concerning the reactivity of the reticuloendothelial system in cases of AFI may serve to clarify this issue.

Klenk and others have studied the structure and quantitative content of certain carbohydrate-linked cerebral lipids in both normal brains and cerebral tissue derived from cases of AFI [24,25]. They have isolated from cerebral gray matter a lipid designated by them as ganglioside which was found to be significantly increased in AFI. These gangliosides were readily differentiated from other cerebrosides by the presence of a complex amino acid-sugar

termed neuraminic acid. On the basis of the fact that this substance (namely, neuraminic acid) was the only tissue compound thus far demonstrably abnormal in AFI, it was felt to be of potential interest to study the serum content of neuraminic acid by technics previously described. Serum neuraminic acid levels were increased in almost all cases of AFI [26]. This finding, however, becomes less important in view of the fact that the substance is also elevated in a wide range of other neurologic and somatic disorders. However, when the serum is partitioned and the neuraminic acid distribution is determined in relation to its protein-fraction linkage, a distinctly abnormal pattern is seen. The ratio formed by globulin neuraminic acid to total neuraminic acid is uniformly abnormal in AFI by group statistical analysis and serves to distinguish the disease from most other neurologic entities thus far studied. It is conceivable on the basis of these findings that the abnormalities related to neuraminic acid hold little relation to the independently observed elevation of neuraminic acid within the nervous tissues of AFI. Rather, they may represent an underlying and possibly fundamental abnormality in the globulin fractions of the serum, with consequent redistribution of the protein linkage of this complex carbohydrate-amino acid. If this be the case, the presented evidence would serve to indicate again the possibility of a disturbance extending beyond the neurectodermal changes which have heretofore been considered the sole abnormality in AFI.

#### SUMMARY

Serial biochemical studies were performed in nineteen cases of amaurotic family idiocy (Tay-Sachs disease), one case of Niemann-Pick's disease (NPD) and one case of diffuse sclerosis, at monthly intervals for periods up to thirty months. An attempt was thus made to equate certain consistent changes in serum and cerebrospinal fluid with the clinical and pathologic evolution of these disorders.

Serum aldolase, initially normal in the early phase of amaurotic family idiocy (AFI), became significantly elevated after approximately nine months of clinically evident illness, coincident with the emergence of skeletal muscle atrophy. The latter was believed to be caused by the observed acceleration of lower motor neuron breakdown. In the protracted phase of AFI, the serum aldolase generally regressed to normal

values. A roughly similar pattern was obtained in the case of NPD, which is a disorder presenting a central nervous system anatomic component almost identical with AFI. No comparable changes in serum aldolase were seen in the case of diffuse sclerosis or other long tract or upper motor neuron diseases studied.

Serum GO-transaminase (GO-T) was consistently and markedy elevated during the entire course of all cases of AFI and also in the case of NPD. The hypertransaminasemia tended to lessen during the protracted phase of these disorders. In contrast, the child with diffuse sclerosis (and patients with other neurologic disorders) showed normal or minimally elevated values. High GO-T levels were also noted in the cerebrospinal fluid of the AFI and NPD cases. The cerebrospinal fluid GO-T was depressed in the case of diffuse sclerosis. These data indicate that the extensive and continuing ganglionic disintegration of AFI is sensitively mirrored by elevated GO-T levels in these two biologic fluids.

The total serum neuraminic acid was non-specifically elevated in the three neurologic disorders principally studied, in contradistinction to the singular elevation of this substance in the cerebral tissues of AFI. However, the serum protein-linkage distribution of this substance in these three diseases showed a distinctly abnormal pattern as indicated by the ratios formed by globulin neuraminic acid/total neuraminic acid and globulin neuraminic acid/globulin protein. A significant depression of serum and cerebrospinal fluid gamma globulin also was observed in AFI.

The evidence presented seems to indicate the possibility that the pathophysiologic substrate of AFI may extend beyond the confines of ganglionic degeneration.

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# Pulmonary Embolism and Infarction\*

### A Review of the Physiologic Consequences of Pulmonary Arterial Obstruction

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YEARS of clinical experience have amply demonstrated that embolism and infarction of the lungs are frequent and serious complications of certain chronic illnesses. In fact, the frequency of these pulmonary accidents appears to be increasing [59,164]. In spite of the recognized importance of these conditions, many aspects of the effects of pulmonary, arterial occlusion are not clear, and the clinical diagnosis is often difficult. We have attempted to re-examine the problem of lung embolism with particular reference to the effects on the general circulation and the mechanism of infarction, and to present physiologic explanations of the clinical events insofar as available data permit. The pathologic conditions concerned in the formation of venous thromboses and the origin of emboli will be considered briefly.

Knowledge of venous thrombosis and the physiologic consequences of embolism has been gained almost wholly within the last century. The observations of Laennec [192], published in 1819, may have foreshadowed the recognition of hemorrhagic infarction of the lungs, although he did not realize the precise nature of the condition. From time to time other physicians described pulmonary lesions at necropsy which appeared to be infarcts. However, it was not until 1856 that Virchow [188] revolutionized the concepts of organ infarction and recognized the phenomenon of vascular embolism.

In 1887 Osler [136] discussed the problem of pulmonary embolism without infarction, and he likewise expressed interest in the occurrence of

pulmonary infarction due to thromboemboli when a careful search failed to reveal the origin of the obstructing thrombi. With the emergence of more precise information regarding the physiologic effects of pulmonary embolism and the conditions under which thromboemboli are formed, a more thorough knowledge of this disorder has been acquired.

In order to present the important considerations in the pathologic physiology of pulmonary embolism, a general discussion of the origin of thromboemboli will be useful.

#### VENOUS THROMBOSIS AND THROMBOTIC EMBOLI

Frequency. The importance of thromboembolic disease of the lungs is pointed up by observations of the frequency of the condition. Pulmonary embolism (without regard to infarction of the lung) was noted in 5 to 14 per cent of cases in general autopsy series [1,17,59,72,206]. Moreover, in necropsy series from two custodial institutions, where terminal illnesses are similar to those of the ambient population, the postmortem incidence of pulmonary embolism was 23.1 per cent [128] and 25.7 per cent [184]. In autopsy studies, Moran [129] found pulmonary emboli in 30 per cent of 140 patients with cardiac disease; Kinsey and White reported [96] an incidence of 48 per cent in association with congestive heart failure. It has been estimated that pulmonary accidents caused or contributed to death in one-fourth to one-half of these cases [17,72,129,184].

In parallel with the observed incidence of

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pulmonary embolism, the frequency of infarction of the lung is likewise impressive. Infarction has been reported to follow embolism in 50 to 60 per cent of cases [17,99,129,184]. If, indeed, congestion of the lung encourages necrosis of

from the right side of the heart are smaller and less apt to be lethal [206].

Non-thrombotic materials, such as amniotic fluid [5,176], fat [161], air [7], bone spicules and fragments of organs (such as brain tissue in

TABLE I SITES OF ORIGIN OF PULMONARY EMBOLI

Site	Range of Reported Incidence of Thrombi Causing Pulmonary Emboli (%)	Representative (average) Data from Miller and Berry [123] (%)	
Lower extremity	20.6 to 95 [59,87,113,123,159]	61	
Right side of the heart	10 to 39.3 [59,123,159]	24	
Pelvic area; prostatic veins	30 [128]	15	
Upper extremity	Rare [13,128,201]	0	

the tissue following embolism, patients with heart disease should be especially liable to the development of infarction. This possibility is confirmed by a postmortem study in which 90 per cent of the lungs of cardiac patients with emboli were found to have areas of infarction [72].

It is accepted that the occurrence of pulmonary embolic phenomena is greatest in the older age groups and is unusual before the ages of thirty to forty, except in obstetrical patients or in those with congestive heart failure [27,59, 67,123,201,206]. The increasing incidence of pulmonary embolism may therefore be due largely to the advancing age of the population.

Contrary to earlier views, general hospital series have demonstrated that pulmonary embolism is significantly more frequent in medical than in surgical patients [17,27,59,72]. Sex, race and season of the year do not appear to be important factors in the incidence of the disease [24,59,67,113,123,184,206].

Sites of Origin of Venous Thrombi. Pulmonary emboli usually originate as detached portions of venous thrombi from the lower extremities. Data concerning the exact sites of these clots are inconsistent because of the difficulty of identification of the thrombotic site, and because the exit of detachable thrombi from veins leaves the vessels empty at the time of autopsy. Representative data are presented in Table 1. Emboli

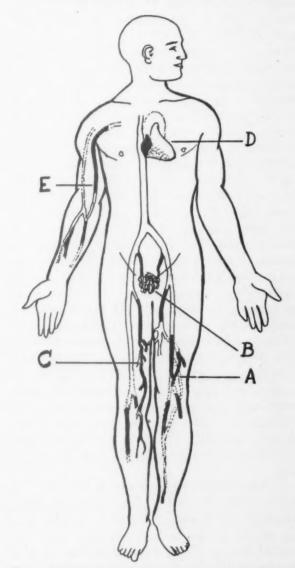


Fig. 1. Diagram illustrating the common sites of venous thrombus formation from which emboli may originate. A and C represent the deep and superficial veins of the lower extremities and B the venous networks of the pelvis. Occasionally, thrombus formation occurs in the right cardiac chambers, D, and rarely in the veins of the arms, E.

severe head injuries [115]) comprise a small percentage of pulmonary emboli.

Venous Thrombus Formation; Role of "Thrombophlebitis." (Fig. 1.) The time-honored theory of thrombus formation (which originated in part with Virchow) has held that retardation of the venous circulation, damage to vessel walls, and

conditions favoring the coagulation of the blood are concerned in the phenomenon of intravascular clotting. This concept remains unchallenged. Cardiac disease with failure is acknowledged to be the most important single condition predisposing to thrombosis [1,16,17,24,59,164], presumably acting by encouraging circulatory stasis [17]. The postoperative state, especially following abdominal and pelvic surgery, is the next most important factor [24,73,164]. Venous stasis is promoted by immobilization, shallow ventilation and by hypotension. Changes in blood coagulation have been described after surgery [24,190], and there may be trauma to the veins in the surgical procedure or in the handling of the patient. Other predisposing causes to thrombus formation are trauma to the lower extremities, especially fractures of the femur [24,59,67], pregnancy, parturition [16,24, 164], polycythemia [67,134], hemiplegia [24], varicose veins [12,24], carcinoma [12,24,82], and possibly obesity [12,67,155,170]. Prolonged bed rest is a frequent contributing influence in these predisposing causes. Hunter et al. [84] found thrombi in the deep veins in many (52.7 per cent) middle aged, normal people who were confined to bed. Simpson [165] observed pulmonary emboli in normal subjects when they arose from long periods of sitting in London air raid shelters, and Homans [80] also reported pulmonary accidents after long automobile rides. Occasionally, there are instances of pulmonary emboli, especially in healthy young men [201], without known predisposing cause [32,113,144,

The conditions which favor the development of thrombi and embolism from the right cardiac chambers are thought to be those causing pooling within the auricular appendage and endocardial damage. The most important of these are congestive heart failure, myocardial infarction, auricular fibrillation and, occasionally, infective endocarditis of the tricuspid or pulmonic valves [21,59,87]. Any type of heart disease leading to congestion or auricular fibrillation may predispose to thrombus formation, either within the cavity of the right atrium or in the peripheral veins [59,129,164].

It has been thought that the detachment of thrombi from veins occurs more readily when the walls are uninflamed (phlebothrombosis). Embolism appeared to be less frequent when venous inflammation had occurred (thrombophlebitis). This concept has recently been criticized [21,24,112]. Byrne [24] stated that all phlebitis is essentially the same process with varying manifestations. As a result, the diagnosis of thrombophlebitis leads, in his opinion, to a sense of security which is not justified. The fact is that any condition suggesting venous clotting, with or without inflammation, should be regarded as the potential source of a serious pulmonary accident.

It is usual for emboli to break away from venous thrombi without apparent cause [49]. However, situations involving ambulation after long bedfastness, straining at stool, or exertion may be attended by detachment of venous clots [49,67,204]. Deep breathing or hyperpnea has been thought to encourage embolism by increasing the rate of venous flow, thereby drawing the floating thrombi to the chest [38,83,111,204].

Once a clot fragment loses its anchorage in the vein, it progresses rapidly through the inferior vena cava and heart into the pulmonary arteries [21,168]. Recent experimental evidence in dogs has indicated that venous emboli may remain in the right ventricular cavity for long periods [194].

Sites of Impaction of Pulmonary Emboli. Obviously, very large thrombi will not progress beyond the larger arteries. In general, smaller emboli pass to the lower lobar arteries of the lungs; embolism of the vessels to the upper lobes is much less common. The right lower lung is the most frequently involved; the left lower lobe is the second site of predilection for embolic occlusion [72,113,123,150,164,184]. The tendency to involvement of the right lower lobe and posterior basal segments in general is thought to be due to the fact that these areas lie in the more direct axial stream of the pulmonary arteries [150,184]. The distribution of these lesions may be useful in differential diagnosis.

#### EXPERIMENTAL PULMONARY EMBOLISM

Experimental observations have clarified the mechanisms of certain physiologic reactions concerned in pulmonary embolism and infarction. In order to bring the entire problem into focus, a number of these studies will be considered briefly.

Extensive Pulmonary Arterial Occlusion. Total obstruction of the main pulmonary artery or of the two principal branches causes rapid death. On the other hand, animals may tolerate the occlusion of as much as 75 per cent of the lung circulation [70,71,74,79,118,174] without death.

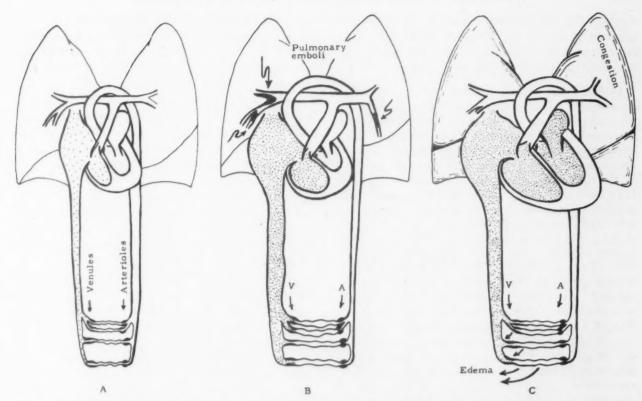


Fig. 2. Diagrammatic sketches illustrating certain circulatory events following acute pulmonary embolism and in congestive heart failure. In normal circulatory balance (A) the output of the left ventricle is conveyed to the myriads of small arteries and arterioles which regulate regional distribution of flow. After arteriolar passage, residual pressure in capillaries, together with sustained venular tone, muscular action and negative intrathoracic pressure, assures a continuing flow of venous blood to the heart. When multiple or massive pulmonary embolism occurs (B), pulmonary hypertension and marked right ventricular strain ensue; however, if sufficient passage of blood through the lungs occurs and left ventricular output is sustained to support life, continued integrity of the arteriolar-capillary-venular system (as in the normal circulation) may maintain venous return to the heart to the extent that severe venous congestion results. Overload and distention of the right ventricle may then be further increased (acute cor pulmonale). Depending upon the degree of pulmonary obstruction and the competence of the right ventricle, cor pulmonale and venous congestion often persist for many hours. Death can occur at any time. (C), when the competence of the left, the right, or both ventricles is reduced by myocardial disease, circulatory insufficiency and venous congestion may be engendered by essentially similar mechanisms. With failure of ventricular output and cardiac dilatation, sustained integrity of the peripheral vascular mechanisms again assures a persistent venous return to the heart and the eventual impounding of blood within the veins. The condition is often chronic so that fluid filtration (edema) of engorged tissues becomes evident as well as other signs of circulatory insufficiency. The increase of blood volume which occurs in chronic heart failure may aggravate the situation.

When critical occlusion of the pulmonary artery occurs, the circulatory events are dramatic. In an open-chest dog preparation, the physiologic aberrations begin when a large foreign body reaches the pulmonary artery. There is a precipitous decline of systemic blood pressure and a concomitant rise in the pulmonary arterial tension. The lungs become white, and the left side of the heart beats in emptiness. Gasping respiratory movements of the chest wall, cyanosis and variable heart rate [122,197] appear, and death supervenes [71,76,79,122,148,197,198].

One of the striking events accompanying acute pulmonary obstruction is the dilatation

of the right cardiac chambers and the turgescence of the peripheral veins [79,122]. These physiologic responses are of interest since they depend on the continued venous return in concert with a diminishing cardiac output. This mechanism of congestion [60] may also operate in the setting of chronic, low-output heart failure [23,63,114,139,146,172,203]. The train of events might be described as follows: The force of the heart beat applied to the blood is dissipated, in part, as it passes the sharp resistance of the arterioles. Nevertheless, after arteriolar passage of the blood column, residual pressure (vis-à-tergo) remains for the propulsion of blood

through the capillaries and venules. In addition, progress of the blood toward intermediate and large veins depends in part upon the sustained restricted calibre of these vessels. (Fig. 2.)

Evidence for the occurrence of venomotion comes from several sources. Combemale [35] reported that, with abrupt cessation of the heart beat of frogs, blood continued to flow in the veins in intermittent rushes, apparently stirred by periodic constriction of the small veins. He concluded that venomotion was essential in the regulation of peripheral circulatory flow. In 1929 Riml [152] observed that sudden cardiac arrest in rabbits was accompanied by brisk, continued blood flow from severed great veins until a large quantity of the blood volume had escaped. Perhaps the most critical experiment has been reported by Rose et al. [157]. They described a specially designed pump applied to the aorta of dogs as a substitute for the left ventricle. The pump drew its supply from a reservoir into which the pulmonary venous blood was directed. The right ventricle was undisturbed, and the preparation could be maintained in circulatory balance with the actual right ventricle, the pump receiving and delivering the same quantities of blood. If norepinephrine were administered to produce a sympathomimetic response, the increased arterial pressure occurring from augmentation of arteriolar resistance increased the quantity of blood displaced from the vascular system and augmented the reservoir volume. Conversely, when sympathetic impulses were inhibited by ganglionic blocking agents, general vascular volume increased and the animal took up a corresponding amount of blood from the reservoir. The changes in vascular volume were so large that participation of the arteriolar and postarteriolar vessels (including the capillaries, venules and small veins) was thought to have occurred as part of the integrated peripheral vascular reaction.

The experimental data described may be transposed to clinical situations. When the outflow from the right ventricle is suddenly curtailed by blocked pulmonary arteries or by left ventricular failure, the right atrium, right ventricle and peripheral veins distend because the heart can no longer accept blood returning through the postarteriolar vasculature. A large portion of the blood volume may then be impounded in the peripheral venous system. Experience has shown that congestive heart failure and severe cor pulmonale from pulmonary embolism are often accompanied by venous congestion, probably induced by the same fundamental mechanisms.

Medium-sized Emboli. In contrast to massive embolization, which can provoke catastrophic effects, single smaller emboli (e.g., to a second-

ary or lobar artery) in normal animals are often relatively innocuous. The fate of the lung tissue following single or multiple small emboli has been repeatedly studied. Karsner and Ash [91] noted that radish seed embolism of dogs was not damaging to the lungs in the absence of pulmonary venous congestion. Mathes, Holman and Reichert [120] found that the lung parenchyma distal to an embolus was often indistinguishable from normal. Other workers have also recorded that small foreign bodies usually produce only minor changes [31,130,154,174]. It is noteworthy that ligation of the main or lobar pulmonary arteries does not result in infarction of the lungs, although some fibrotic change may eventually occur [81,104,120,160].

In contrast, the effects of single lung emboli are different when the circulation of the lungs has been previously compromised. To explain these differences, the general circulation of the lungs requires more detailed consideration.

The Dual Bronchopulmonary Circulation. The lung tissue possesses a dual vasculature which permits the tissue to fall back on the alternate bronchial arterial source of blood when the pulmonary artery circulation is obliterated. In man, the bronchial arteries usually arise from the aorta or one of the first two intercostal arteries [30,124]. In the dog, the major bronchial vessels often originate from the fifth or sixth right intercostal artery [22]. The study of bronchial arterial function and flow has been difficult because of the variability and inaccessibility of these structures [120,174]. It is known that these vessels follow the course of the bronchi into the lung parenchyma, where they branch elaborately and rejoin to form plexuses around the bronchi and in the bronchial submucosa. External to the lungs, they supply the vasa vasorum of the pulmonary artery, the vagi and the mediastinal structures through anastomoses with numerous other vessels [18,30,42,183]. (Fig. 3.)

Occlusion of the bronchial artery has been shown to produce ischemia and necrosis confined to the tissue of the main bronchi at the hilar area [54]. However, the arteries are known to extend to the respiratory bronchi and alveoli [18,124]. Indeed, Cudkowicz and Armstrong [42] suggested that they supply all the lung tissue except the pulmonary capillary epithelium. The major portion of the blood from the bronchial arteries returns via the pulmonary veins [18,124]. The bronchial veins also form a plexus

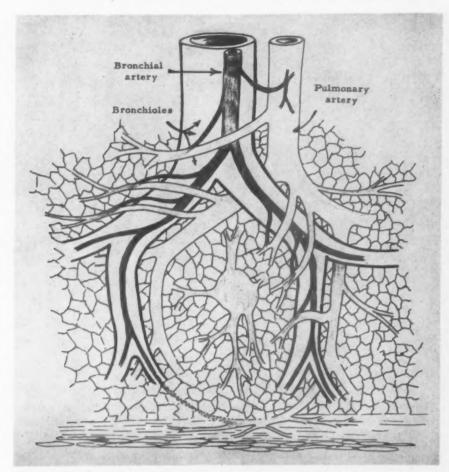


Fig. 3. Diagrammatic sketch, modified from Verloop [185], illustrating the circulation of the normal lung. The illustration shows the precapillary connections between the pulmonary and bronchial arteries, and the collecting pulmonary vein at the center of the lobule. The blood supply of the visceral pleura (bottom) is provided by extensions of the pulmonary and bronchial arterial systems.

around the bronchi, draining into the azygos, hemiazygos and intercostal venous systems [124], and anastomose widely with the pulmonary veins [119].

The pulmonary arteries are extensively anastomotic between themselves at the capillary level [119]. The existence of precapillary anastomoses between pulmonary and bronchial arteries has been debated [54]. Several observers believe that bronchopulmonary communications are limited to vessels of capillary size [18,42,125]. However, the weight of evidence now suggests that precapillary connections between the systems are present and that these anastomoses may become greatly enlarged under certain conditions of disease [106,119,151,183,185].

The mechanism of expansion, or enlargement, of the bronchopulmonary "bridging arteries" is not clear [105]. However, it is certain, from clinical and experimental observations,

that diminution of pulmonary arterial inflow into a segment of the lung (whether by embolism or by arterial ligation) will incite a substantial development of the bronchial collateral circulation in the area [81,88,104,160]. It has been suggested that marked diminution of pulmonary arterial pressure and resistance distal to the point of obstruction permits blood to flow into the pulmonary vascular bed from the connecting bronchial arteries which gradually enlarge to accommodate this flow [92,105]. It is also possible that the enhanced capacity of these collateral channels occurs under the same conditions which prevail in other injured tissues to induce vasodilatation.

The contrast between the capacity of the normal and expanded collaterals is striking. By direct cannulation of the bronchial arteries in dogs, Bruner and Schmidt [22] noted that the normal arterial flow averaged 5 cc. per minute

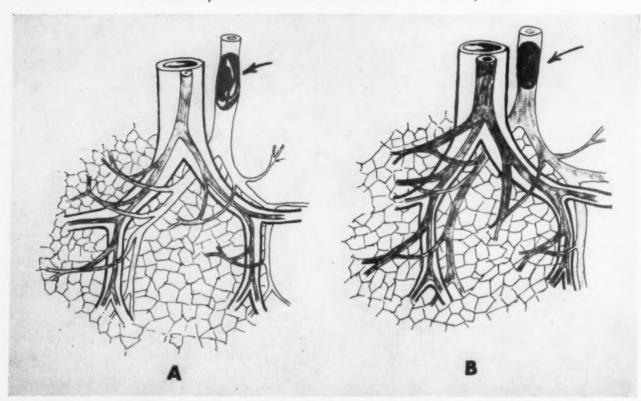


Fig. 4. A, diagrammatic illustration of the bronchopulmonary circulation of the lung immediately after an embolus (arrow) has lodged in the pulmonary artery. B, diagram of the dilatation of the bronchopulmonary arterial connections in a period of days after the embolic impaction. Bronchial arterial blood now enters the pulmonary arteries distal to the embolus to sustain the integrity of the lung tissue.

(less than 1.0 per cent of cardiac output). Although approximately two-thirds of the bronchial blood enters the pulmonary veins, the admixture of this small quantity is not sufficient to lower net oxygen saturation of the pulmonary venous blood [22]. Various other methods for the measurement of bronchial arterial flow have been devised. One simple technic entails the collection of blood from a lobar artery or vein after the corresponding pulmonary artery has been occluded. Blood escaping from the cannulated vessel is derived from the bronchial inflow to the lobe [141,163,199]. Using this procedure in dogs, collateral irrigation is generally less than 1.0 cc. per minute shortly after ligation of the corresponding pulmonary artery [141,163]. However, the collateral flows increase to 16 to 26 cc. per minute [141] or more [199] in four to seven weeks after obstruction of the lobar artery. The enlargement of the collateral bronchial arterial system resulting from pulmonary embolism is therefore slowly progressive for several weeks or longer [141]. The bronchial artery supply of blood varies directly with the systemic blood pressure [141,199]. Another

technic for the measurement of the collateral circulation (Liebow et al. [105]) utilized the oxygen uptake in the segment of the lung which was deprived of pulmonary arterial blood. The accessory flow increased significantly within two weeks after ligation of the left main pulmonary artery and often attained levels as high as 1 L. per minute (a forty-fold increase over normal) over a period of four months [19]. Since most of the ancillary lung flow returns to the pulmonary veins, it was estimated that the left ventricular load was increased as much as onethird over that of the right ventricle [19]. Further evidence of augmentation of bronchial collateral flow within seven to fourteen days after occlusion of a pulmonary artery is obtained by the injection of neoprene latex, or other contrast medium, into the aorta, whence it rapidly fills the whole of the pulmonary vasculature (distal to the obstruction in the pulmonary artery) through the dilated bronchial vessels. In the absence of previous occlusion of the pulmonary artery, the bronchial arteries are small, and the contrast substance does not reach the pulmonary arterial branches from the aorta

[105,141]. (Figs. 4 and 5.) These various experiments provide sound evidence that the bronchial circulation may increase greatly, perhaps sufficiently to sustain the parenchymal tissue when pulmonary blood flow is interrupted. As a result, the parenchyma distal to the occlusion may be preserved, so that there is neither gross nor microscopic evidence of infarction.

The clinical counterparts to these experiments are likewise of interest. In bronchiectasis, pulmonary embolism and infarction, abscess of the lung, tuberculosis, primary tumors of the lung, and in certain kinds of congenital heart disease, marked dilatation of the bronchial arteries may occur, to as much as ten times their original size [33,41,105,202,205].

As the bronchial arteries dilate to form a collateral circulation for the lungs, the bronchial veins probably also accommodate the increased carriage of blood. Conspicuous dilatation of the bronchial veins often occurs in emphysema and in mitral stenosis [52,103,202]. In conditions calling forth the collateral vascular system of the lungs, the resultant enlargement of the bronchial vessels may become the source of dangerous hemorrhage [58,105,202].

Infarction of the Lungs. Pulmonary infarction does not result from ligation of the lung arteries, and is unusual after embolization in animals with normal lungs. Numerous studies have indicated that some alteration of the intrinsic circulation of the lungs must be present to induce tissue necrosis after obstruction of a pulmonary artery. Many years ago Karsner and Ash [91] described the occurrence of infarction in dogs when embolic arterial occlusion was produced in lungs previously congested by ligation of lobar veins, or by compression from artificial pleural effusions. Mathes et al. [120] likewise observed hemorrhagic consolidation, and even gangrene, after the introduction of infected emboli. Their experiments indicated that combined infection and embolism of the lung so damaged the vascular structures that frank tissue necrosis occurred. Moses [130] bound the chests of rabbits tightly so as to invoke stasis within the lungs; thereafter, embolism was usually followed by extensive infarction. Other workers [31,154] have obtained generally confirmatory results. Based on such observations, it has been generally accepted that pulmonary congestion, infection and diminished ventilation [154] promote pulmonary infarction by inviting intrapulmonic circulatory stasis [37], which so impedes irrigation



Fig. 5. Photograph of the lungs of a dog. During life, a segment of No. 6 (French) urethral catheter was introduced into an external jugular vein and the embolus lodged in the left lower lobar artery (arrow). Seventeen days later the lungs were removed after injection of the bronchial arteries (through the aorta) with barium sulfate suspension. The lungs were then dehydrated in alcohol and cleared in oil of wintergreen. The bronchial arteries are clearly visible in the right upper lobe as long vessels with few branches. Note penetration of barium suspension into finer pulmonary arteries in the left lower lobe (distal to the embolus), indicating that the bronchial arteries functioned as a collateral blood supply.

through the connecting bronchial arteries [85] that the benefits of the collateral blood supply are largely annulled. (Fig. 6.)

These general concepts of the genesis of pulmonary infarction have been supported by further study. Parker and Smith [141] constructed femoral arteriovenous fistulas in dogs and thereafter subjected the animals to pulmonary embolization with short segments of rubber catheter. Infarction was usually present at autopsy. In these "fistula dogs" the lesion occurred presumably because the bronchial collateral circulation failed to function or failed to expand. However, when the pulmonary and bronchial arteries of the infarcted lobes were injected with liquid latex it was evident that the

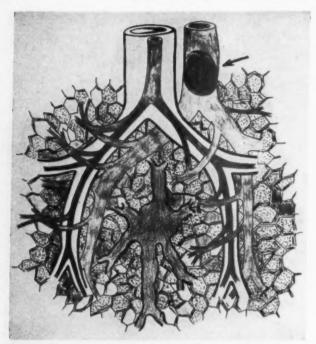


Fig. 6. Possible mechanism of formation of an infarct of the lung. The picture shows a thrombotic embolus (arrow) in the pulmonary artery of the lung segment. The presence of passive congestion of the tissue (from any cause) is illustrated by the distended pulmonary vein in the center of the lobule. The bronchopulmonary anastomoses are normal or enlarged, and the collateral circulation is anatomically intact. However, it is presumed that the collateral circulation has been defeated by impairment of venous drainage (by congestion), permitting breakdown of the tissue distal to the embolus to occur.

bronchial vessels were as greatly enlarged as in normal lungs following pulmonary arterial occlusion. Furthermore, when the bronchial lobar flow was measured four to seven weeks after the embolization the collateral flow had reached 16 to 26 cc. per minute. Therefore, there was sound evidence that lung tissue undergoing the changes of infarction may be possessed of an anatomically adequate system of collateral vessels [141]. It was assumed that interference with the function of the ancillary vasculature by an A-V fistula rendered it incapable of nourishing the tissues. It has not been possible to explain precisely the mechanisms by which peripheral arteriovenous shunts can so curtail the function of the accessory circulation. The interposition of a shunt in the general circulation (before the collateral vessels have become enlarged) may decrease bronchial arterial flow because of lowered systemic blood pressure or because of compensatory vasoconstriction in the bronchial arterioles due to the low-resistance fistula.

Contrary to these concepts of the mechanism of infarction, other observers [55,163] have suggested that development of the bronchial arterial collaterals actually encourages the formation of infarcts following embolization. They believe that blood from the enlarged bronchial vessels in the embolized lobe is forced, under systemic pressure, into the anoxic alveolar capillaries, producing a destructive effect and causing hemorrhage and necrosis. Ellis and his associates [55] postulated that intercapillary anastomoses of the pulmonary arteries themselves form the greater part of the collateral circulation. They produced occlusion of the bronchial artery to the right upper lobe in dogs, and noted that subsequent glass bead embolization did not cause infarcts of that lobe although infarcted areas occasionally formed in other lobes which were more heavily embolized. They also reported that pulmonary emboli provoked infarction when corresponding lobar veins were ligated whether or not the bronchial arteries to the part were also occluded. The results implied that the bronchial arteries are not essential in sustaining the nutrition of the tissue when pulmonary arterial flow is shut off. It has been difficult for us to accept the interpretations of Ellis et al. [55] and of Shedd and his co-workers [163] in view of the marked augmentation of collateral bronchial flow in embolized lobes in which necrosis did not occur [141]. On the basis of their hypothesis it is also difficult to explain why infarction does not occur after lobar arterial ligation, if pulmonary intercapillary anastomoses do form the basic collateral circulation. In the light of present information we prefer to accept the working hypothesis that, when lobar embolization occurs, expansion of the bronchial collateral vasculature ordinarily serves to sustain the lung and prevent the development of an infarct; however, when embolization occurs in the presence of congestion, infection or other conditions which may interfere with bronchial arterial flow, infarction may occur even though the accessory vasculature has been augmented throughout the affected parenchymal area.

Whatever the mechanisms involved, the circumstances of occurrence of experimentally produced infarction of the lung find an interesting counterpart in clinical medicine. It is indeed the patient with pulmonary congestion (whether from heart failure [21,99], prolonged inactivity [117] or local pulmonary disease [28,86]) who is more subject to pulmonary infarction as the result of thromboembolism. This knowledge conforms to the experimental evidence that marked or even subtle imbalances of the movement of blood through the lungs are sufficient to nullify the beneficial effects of a collateral circulation, regardless of how extensive the collaterals appear to be.

That total failure of the blood supply to the lungs also results in rapid breakdown of lung tissue is demonstrated in experiments using infected emboli [120]. Another experiment entails the use of emboli made of cotton which is soaked in croton oil (an intense tissue irritant) and placed in a gelatin capsule. Impaction of this embolus in a lobar artery provokes no immediate symptoms. However, within twenty-four to fortyeight hours cough and evident illness usually develops in the animal. Autopsy shows extensive liquefaction necrosis (gangrene) of the embolized lobe. Furthermore, injected contrast media will not enter the involved tissue either through the bronchial or pulmonary arteries. Therefore, the gangrenous changes clearly result from acute total destruction of the lobar blood supply [142]. There is a striking difference between necrosis of tissue which leads to an infarct and that which results in gangrene. In the case of the lungs, infarction involves tissue injury with sufficient preservation of blood supply to sustain fibrotic repair. Gangrene represents total deterioration of tissue from complete destruction of the lung vasculature. Fortunately, the latter condition is rare. (Fig. 7.)

Vascular Responses Provoked by Miliary Embolization of the Lungs. It is well known that embolization of the lungs with particulate matter invokes severe pulmonary hypertension, a decline of systemic blood pressure, and death with distention of the right cardiac chambers and engorgement of the peripheral veins. Actually, these dynamic effects are little different from the effects produced by occlusion of the main pulmonary artery. The genesis of the pulmonary hypertension from miliary embolism has remained controversial. Some investigators have postulated that particulate embolism induces reflex pulmonary arterial constriction [25,48,76,78,94,133,148]. This suggestion has been invoked to explain the deaths of patients when pulmonary emboli block only a minor portion of the pulmonary arterial bed [48,49,59,69,93,184]. This explanation has also been predicated upon the occurrence of marked elevation of pulmonary pressure after embolization with barium sulfate, lycopodium spores or other divided matter in quantities that seemed insufficient to account for the reactions as simple blockade of the lung vasculature. As an example, in the innervated heart-lung preparation (with intact central nervous system) it was noted that barium embolization of the lungs caused abrupt pulmonary hypertension

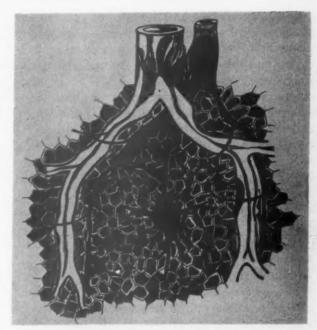


Fig. 7. Illustration of the possible mechanism of pulmonary gangrene. When the blood supply of the lung tissue is critically diminished or totally obliterated by occlusion of both the pulmonary and bronchial arteries to the part, liquefaction necrosis (or gangrene) ensues.

and diminished left ventricular output, with invariable death of the preparation [148]. However, when the lungs were denervated at the height of this embolic reaction by elimination of the circulation to the nervous system, pulmonary hypertension gradually subsided, left ventricular output increased, and the preparation survived. When hexamethonium was administered to the innervated heart-lung preparation, or if the upper four or five thoracic sympathetic ganglia were removed, the introduction of barium into the pulmonary arteries did not produce abrupt pulmonary hypertension unless larger quantities of the material were injected to produce mechanical block. These experiments [148] suggest that miliary embolization of the lungs invokes widespread constriction of the pulmonary arterioles, mediated through sympathetic impulses. As an interesting corollary, Villaret, Cachera and Fauvert [187] observed constriction of the minute pial arteries in dogs following miliary embolism of the carotid arteries. It seems possible that pulmonary arterial constriction also results from particulate emboli. Aside from the problem of embolism, other work has demonstrated that the lesser circulation is capable of active vasoconstriction [6,145,157,178] through autonomic stimuli.

On the other hand, a number of observers

[3,38,39,44,68,71,76,79,122,198] have concluded that the methods described do not obviate the possibility that miliary embolism merely produces multiple mechanical obstructions of the finer lung vessels. Williams [198] noted that dogs subjected to embolism with glass beads (60 microns) showed a gradual rise of pulmonary arterial pressure with increasing numbers of beads. The resulting pulmonary hypertension was not abolished by hexamethonium. He concluded that evidence of reflex vasoconstriction was lacking and that elevation of pulmonary tension was the outcome of simple arterial blockade.

It is clear that the question of pulmonary vasomotion from embolism has not been resolved in spite of the many efforts to elucidate the problem. Nevertheless, it seems probable that the effects of most pulmonary emboli on the circulation of the lungs are largely mechanical. In instances in which smaller vessels are embolized by fragmented clots or amniotic fluid, pulmonary vasomotor responses may be an important additional means of bringing about a catastrophic circulatory shutdown [25].

Recently, a growing appreciation of the effects of serotonin (5-hydroxytryptamine) on the circulation has led to investigations of its role in pulmonary vasomotion. Serotonin apparently provokes a vasoconstriction of the lung arteries in cats and dogs [36,158,167]. Comroe et al. [36] postulated that certain vascular disturbances of pulmonary embolism may result from local or reflex reactions to serotonin when it is released from platelets during the coagulation of blood. However, Nemir et al. [132] found no rise in pulmonary arterial pressure in man when serotonin was injected distally into an occluded pulmonary artery. The precise role of this interesting substance in pulmonary vascular accidents needs clarification.

The presence of large arteriovenous shunts in the pulmonary circulation has been the subject of some discussion. Several workers [133,149,183] have reported the existence of A-V connections up to 500 microns in size; others [44,64,98] have been unable to reproduce these results. The principal evidence for the presence of pulmonary A-V shunts is that glass spheres, of a size up to fifty times that of capillaries, may be recovered from the pulmonary veins after their introduction into the pulmonary artery [183]. Recently,

Parker, Andresen and Smith [140], employing a somewhat different technic in dogs, have been able to recover lucite spheres 75 microns in size, which passed through the arteriovenous circulation of the lungs. However, spheres of 250 to 350 microns apparently did not pass through the lung vasculature. These experiments confirm the presence of functional A-V shunts in the pulmonary circuit, although the exact sizes of the communications are left in doubt. Niden and Aviado [133] suggested that these shunts may lessen the rise of pulmonary arterial tension after embolization but, because of the circumvention of blood through them and the consequently lowered capillary flow, they may also aggravate

the resulting anoxemia.

Vascular Lesions from Fibrin Emboli. Clinical [15,29,135,138] and experimental [14,51,52,75,77, 131,181,182,191] observations have suggested that embolism with fine clots or with fibrin induces significant pulmonary arterial lesions. For instance, when macerated fibrin suspensions were administered intravenously to rabbits, the fibrin, caught in the finer pulmonary vessels, was incorporated into the vascular intima. The process produced an eccentric fibroelastic thickening of the intima closely resembling the lesions of atherosclerosis [181]. It has been suggested that pulmonary hypertension or other mechanical factors are important in inciting these lesions [57]. Thomas et al. [181] have shown that embolism of rabbits with glass beads does not result in the development of atherosclerotic-like lesions although pulmonary hypertension develops following the embolization. Parker, Thomas and Smith [143] administered fine suspensions of fibrin to dogs intravenously, twice weekly for six weeks. These dogs did not exhibit pulmonary hypertension but at autopsy showed well defined intimal lesions resembling those of atherosclerosis; pulmonary hypertension per se evidently was not responsible for the specific pathologic process in the vascular walls. The pathogenesis of these lesions, produced by fibrin deposition, requires further study. They bear a striking resemblance to the amerosclerotic processes found in the pulmonary arteries of some patients with mitral stenosis and other diseases causing pulmonary hypertension. The suggestion has been made that "idiopathic" pulmonary hypertension and pulmonary arteriosclerosis may result from repeated pulmonary fibrin emboli [138].

INTERPRETATION OF THE CLINICAL MANIFESTATIONS OF PULMONARY EMBOLISM AND INFARCTION

The manifestations of embolism of the pulmonary arteries and of necrosis of the lung tissue

Table II
CLINICAL EVIDENCES OF PULMONARY EMBOLISM
IN APPROXIMATE ORDER OF IMPORTANCE
AND FREQUENCY

Manifestations of Pulmonary Embolism:

Dyspnea

Substernal oppressive chest pain

Tachycardia

Manifestations of cerebral ischemia

Restlessness, anxiety

Syncope

Convulsions

Electrocardiographic changes

Shock

Evidence of right-sided cardiac dilatation and failure

Fever

Sudden death

Note: Embolism may be

Silent Varied in symptomatology Recurrent

Table III
CLINICAL EVIDENCES OF PULMONARY INFARCTION
IN APPROXIMATE ORDER OF IMPORTANCE AND
FREQUENCY

Manifestations of Pulmonary Infarction (Possibly preceded by evidence of acute embolism):

Pleuritic chest pain

X-ray densities

Fever

Hemoptysis

Cough

Dyspnea

Tachycardia

Elevated leukocyte count and erythrocyte sedimentation rate (non-specific)

are often not separated in clinical descriptions. However, infarction of the lungs does not necessarily follow embolism, and uncomplicated emboli often cause distinctive clinical manifestations. Therefore, the two processes will be considered separately in so far as possible. Tables II, III and IV list the salient features of embolism and infarction of the lung, but it should be realized that many symptoms are common to both. The "classical" clinical picture of pulmonary throm-

boembolism has usually been described as precipitate dyspnea, pleuritic or oppressive chest pain, and cough and hemoptysis. Although this whole symptom complex is often present, producing a striking clinical picture, any one of the individual symptoms may predominate

Table IV
OCCASIONAL FEATURES OF PULMONARY VASCULAR
ACCIDENTS WHICH MAY BE HELPFUL IN
DIAGNOSIS

Suggestive Diagnostic Manifestations of Pulmonary Thromboembolism:

Unexplained fever

Fever not responding to chemotherapy [32,67,87]

Increase in severity of congestive heart failure [67,87]

Paroxysmal arrhythmias [83,201]

Tachycardia, digitalis toxicity and mercurial-fast edema in patients with congestive failure [180]

Unexplained bloody pleural effusion [32,87]

Appearance of lung abscess on x-ray [34,101]

Unexplained leukocytosis

in any given case, and in other instances there are no symptoms at all [16,50,87,123].

#### PULMONARY EMBOLISM

Effects of Embolization of the Larger Pulmonary Arteries. Embolic occlusion of the main pulmonary arterial trunks is usually rapidly fatal [50,65]. However, in the case of smaller single or multiple thromboemboli the ensuing circulatory events can be observed. The resulting physiologic mechanisms are complex and difficult to describe. It is well to remember that the manifestations of embolic episodes are exceedingly varied [15]; furthermore, the emboli tend to be recurrent [16,65,87,159,201] so that changing patterns of symptomatology are evident. Basically, the impaction of large emboli elicits responses which are almost entirely referable to mechanical obstruction of blood flow through the lungs.

Dyspnea is one of the common symptoms of pulmonary embolism. It often begins suddenly and progresses rapidly to gasping respiration. On the other hand, it may be mild and evanescent. Dyspnea of varying severity was the presenting symptom in 25 and 42 per cent of cases, respectively, in two series of observations [49,59]. Labored breathing may also begin after infarction has developed [123]. Miller [123] reported that dyspnea occurred as the sole complaint in 20 per cent of his cases. When shortness of breath becomes suddenly manifest in cardiac

or bedridden patients, and particularly when the dyspnea is disproportionately severe, the possibility of pulmonary embolism should be

entertained [21,67,87].

The fundamental mechanism of dyspnea in relation to pulmonary arterial occlusion is not completely known [201]. The difficult breathing has been variously explained by anoxia [133] or by reflexogenic effects resulting from stimulation of receptors in the pulmonary artery, right side of the heart and superior vena cava [121]. In some cases the resultant pulmonary lesion becomes analogous to pneumonia, in that anoxia occurs from lack of aeration. The resulting hyperpnea causes the carbon dioxide tension of the arterial blood to fall below normal, producing a moderate alkalosis. The respiratory center is thus stimulated. Fever, if it occurs, may accentuate the hyperpnea by increasing the rate of tissue oxidation. Among the reflexogenic stimuli which possibly contribute to labored respiration are those of the Hering-Breuer type. These reflexes are actuated by collapse and distention of the alveolar spaces and air ducts, so that inflation of the lung initiates expiration, and deflation inhibits expiration and stimulates inspiration. It is not unlikely that other reflexes, similar to the Hering-Breuer phenomenon, are set up in the process of distention of the vascular channels from impaction of the embolus itself. Finally, the psychological impact of the accident is often marked, so that apprehension or fright adds to the respiratory distress [21,201].

The appearance of chest pain with embolism and infarction of the lung is a symptom of importance. Pain was the most frequent complaint of patients in Sagall's study [159] of the condition, and it was the initial symptom of embolism and infarction in 12 and 32 per cent of cases, respectively, in other reports [49,59]. In some patients, chest pain is not prominent or is absent altogether [123]. As a general rule, the pain in pulmonary infarction is of pleuritic type [159]; in association with embolism, the discomfort is often substernal and similar to the pain

of myocardial ischemia [65].

The possible causes of substernal discomfort in pulmonary embolism are of interest. At one time it was considered that embolic impaction provoked reflexogenic constriction of the coronary vasculature, producing myocardial ischemia and pain. However, it is now considered more probable that the mechanical block to blood flow through the lungs, the lowered blood

pressure and the resulting decreased cardiac output reduce coronary flow. In addition, pulmonary hypertension and distention of the right cardiac chambers interfere with the outflow of blood from the various coronary venous channels [43,122,189,201,204] and, in turn, impair the general coronary circulation. The resulting coronary insufficiency is the probable cause of the angina-like pain. Other mechanisms of chest pain following embolization have been suggested. The thoracic pain may reside in the distention of the pulmonary artery due to the embolic obstruction [65,201], since experimental evidence indicates that tension applied to arterial walls induces severe pain [66,166]. Pain of anginal type has been reported in chronic pulmonary hypertension [186], and it would not be unexpected in the course of acute pulmonary arterial dilatation from thromboembolism.

When thromboembolism blocks off the blood supply to a large portion of the respiratory tissue, hypoxia results and, particularly if associated with shock, cyanosis appears. In one study cyanosis was present as the initial objective sign of embolism in 24 per cent of patients [49]. The occurrence of anoxia also has been attributed to the opening of pulmonary arteriovenous shunts [133] or to extreme dilatation of the capillaries remaining open and the rapid passage of blood

through them [198]. In many subjects, pulmonary embolism is promptly followed by signs of circulatory collapse. Evidently the acute impairment of pulmonary blood flow, causing critical reduction of left ventricular input, induces a decline of the systemic circulation with resultant cerebral ischemia and shock. Krause and Silverblatt [99] emphasized the appearance of restlessness and apprehension in over half of their cases, as evidence of diminution of the cerebral circulation. In fact, these symptoms frequently preceded other evidence of a major embolic catastrophe. Other observers [67,159] have described coma, weakness, profuse sweating and convulsions as the outcome of cerebral ischemia following pulmonary embolism. Transient loss of consciousness, resembling syncope, and loss of sphincter control with an overwhelming urge to defecate have also been reported [99,123]. In a few patients the symptoms of cerebral disorder are the only manifestations of the pulmonary accident [21,59]. These general symptoms seem clearly referable to the inordinate activity of the autonomic nervous system that frequently

accompanies critical diminution or failure of the circulation to the central nervous system.

The advent of shock from the embolic assault can be sudden and fatal [65]. Shock has been reported to occur in as many as 25 per cent of patients with pulmonary emboli, and it may be the initial sign of the accident [49,59,159]. It is understandable that the underlying cause of the shock may be mistaken for acute coronary occlusion [49,159]. Sudden death has been reported in from 3 to 14 per cent of cases of thromboembolism [59,123,159]. The mechanisms concerned in the etiology of circulatory collapse are not fully understood. It seems certain that abrupt diminution of cardiac output (due to the pulmonary obstruction) and right ventricular insufficiency are important contributing events. In addition, it has been observed time and again that critical injury or ischemia of certain organ systems will incite marked dilatation of the peripheral vasculature and shock. This reaction, like that often following myocardial infarction, probably takes place through the mediation of reflexes. It is presumed that such reflex mechanisms induce the generalized vasodilatation, hypotension and circulatory collapse that may ensue

Tachycardia is another of the more constant signs of pulmonary embolism and infarction. Persistent rapid heart rate has been observed in the majority of patients with known embolic pulmonary disease [32,123,159]. Since increase in the frequency of heart beat is one of the mechanisms for augmentation of cardiac output, tachycardia should be expected in the vascular collapse, anoxia and fever that commonly complicate pulmonary accidents.

The resultant breakdown in cardiac function occasionally provides the most dramatic evidence of massive embolism. Under the impact of the pulmonary hypertension, acute dilatation of the right ventricle occurs. The extent and rapidity of ventricular embarrassment is directly dependent upon the degree of obstruction of the lungs, and it is at this point that distention of pulmonary arteries and even the normal heart may become extreme. The condition is suggested by prominent pulsation along the right sternal border, together with a loud pulmonic second sound, a pulmonic systolic murmur and diastolic gallop rhythm. Because of the continued venous inflow to the heart (unless frank shock has occurred) the peripheral venous system becomes engorged, and cyanosis is intensified. If massive embolism

is sustained, the acute or gradual development of right ventricular failure occurs [99,196]. Infrequently, chronic cor pulmonale results from repeated pulmonary embolism and increasing impedance to blood flow through the lungs [45,138].

The appearance of paroxysmal cardiac arrhythmias, particularly auricular fibrillation, auricular flutter and supraventricular tachycardia [83,201], increases the threat of collapse. Possibly these are related to marked stimulation of the autonomic nervous system in conjunction with pre-existing myocardial disease, or the anoxia and cardiac strain engendered by the embolism itself.

It is important to appreciate that even the most careful physical and laboratory examination may reveal no indication of pulmonary embolism in many instances. Historical and physical evidence of venous thrombosis is evident in less than 50 per cent of cases; however, the possibility should be carefully explored in any patient with presumed pulmonary inflammatory disease [8,32,47,59,67,123,144,155].

Electrocardiographic Signs. The electrocardiographic changes in pulmonary embolism have been extensively studied [110,171]. Frequent tracings are essential if the procedure is to be useful [11]. Wolff [201] stated that careful electrocardiographic observation will reveal transient changes in three-fourths of patients with significant embolization. However, Miller and Berry [123] have reported important electrocardiographic changes in only fifteen of thirty-seven patients. Baker et al. [8] found cardiographic alterations in 11 per cent of their cases—a very low incidence (Figs. 8 and 9.)

The typical electrocardiographic alterations following pulmonary embolism are set forth in Table v. It is generally held that the typical patterns in embolism are the result of acute strain and dilatation of the chambers of the right side of the heart [99,110,123]. The presence of Q waves in leads II and III and AVF, with inverted T waves, as may occur with pulmonary embolism, may erroneously suggest posterior myocardial infarction. Karlen and Wolff [89] believe that vector cardiography may be useful in differentiating these two conditions.

Radiographic evidence of pulmonary embolism (without tissue infarction) is occasionally recognized by the appearance of abrupt termination and dilatation of a large pulmonary arterial shadow. In addition, there may be increased

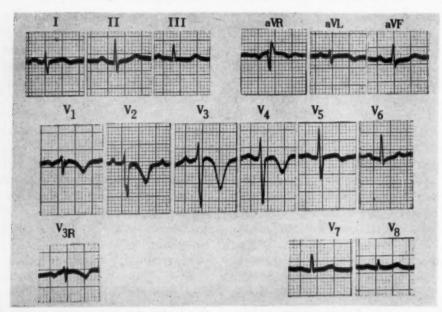


Fig. 8. Electrocardiographic tracing demonstrating some of the changes of pulmonary embolism. Note S-1, large R wave in lead AVR, incomplete right bundle branch block, clockwise rotation of the heart, and deeply inverted T waves in precordial leads V-1 to V-4. (Courtesy Dr. Edward Massie, Heart Station, Barnes Hospital.)

radiolucency of a localized portion of the lung field resembling emphysema [162,169,195,200,201]. The difficulty of recognition of these changes is illustrated in an experimental study of chest roentgenograms taken before and after embolization of the lungs of animals. There were no

TABLE V
ELECTROCARDIOGRAPHIC CHANGES WHICH MAY
OCCUR FOLLOWING ACUTE PULMONARY
EMBOLISM

S<sub>1</sub>-O<sub>3</sub> pattern

Development of S1, S2, S2

ST segment depression in leads 1 and 11

Appearance of right axis deviation and change to vertical heart position

Flat or inverted T waves in leads II and III Peaked P waves in leads II, III and AVF

Development of marked clockwise rotation of the heart Appearance of right bundle branch block or right ventricular enlargement patterns

Inverted T waves with ST segment deviations in the right precordial leads [11,99]

radiographic changes of any kind noted after the embolism [97]. The essential value of the chest roentgenogram has not been fully established in terms of pulmonary embolism without infarction; nevertheless, the examination may be of occasional worth for the reasons enumerated. Angiographic technics have been reported to demonstrate dilatation or obstruction of a pulmonary artery proximal to an embolus [4,108].

The foregoing clinical descriptions apply particularly to relatively massive pulmonary emboli. The impaction of one or more thrombi in the smaller arteries usually incites less violent symptoms or none at all.

#### PULMONARY INFARCTION

The conditions for the genesis of lung infarction in man appear to be fundamentally similar to those which induce the complication in the experimental animal. Embolic arterial obstruction leads to hyperemia and edema of the lung tissue in man [90,127]. If the general circulation of the lung has been previously disturbed, embolism invites the onset of insidious necrosis of the parenchyma. The infarcts are usually less than 5 cm. in diameter, and are roughly triangular in outline with the base at the pleural surface. In twenty-four to forty-eight hours more or less hemorrhage into the alveolar tissue occurs. Thereafter, the affected area becomes distinctly demarcated, hemorrhagic and consolidated. On microscopic examination, there is some alveolar wall necrosis, so that the saccular partitions become shadowy or disappear. Within a space of two weeks fibroblastic repair begins, and new capillaries penetrate

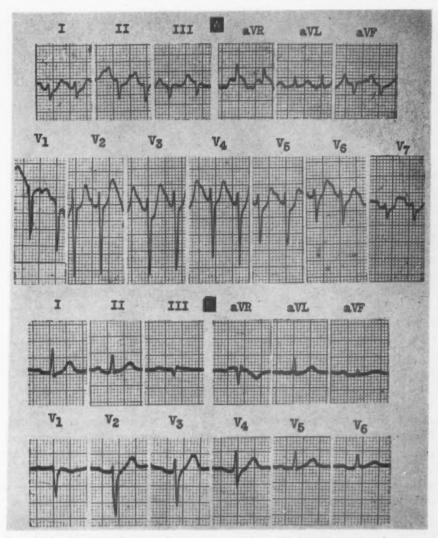


Fig. 9. A, electrocardiogram in acute cor pulmonale secondary to pulmonary embolism. There is an S-1 Q-3 pattern, large R wave in lead AVR, auricular tachycardia, marked clockwise rotation of the heart, and low to absent R waves in leads II, III and AVF which would suggest posterior myocardial infarction if pulmonary embolism were not known to be present. B, electrocardiogram of the same patient twenty-four hours later. Sinus mechanism has been restored, and the record has returned to normal. (Courtesy of Dr. Edward Massie, Heart Station, Barnes Hospital.)

the affected site from the edge. Fibrosis advances rapidly, hemorrhage is resorbed, and the necrotic tissue is replaced by shrunken fibrotic scarring. In some cases all evidences of a previous infarct disappear. In other instances pleural thickening and adhesions persist as remnants of the process [67,90,99,127]. A recent suggestion that proliferation of epithelium on the border of pulmonary infarcts may lead to carcinoma of the lung requires confirmation [10].

Specific Clinical Manifestations of Pulmonary Infarction. Clinical evidence of infarction of the lungs often appears suddenly. The embolic

event which preceded the lesion may or may not have excited symptoms in itself.

The most important symptom of infarction is pleuritic chest pain [113] due to fibrinous inflammation of the contiguous pleurae. The origin of this pain is clear. Since the parietal pleura is highly sensitive to pain stimuli [26], the development of pleuritis in the process of pulmonary necrosis provokes knife-like, cutting pain on thoracic movement. The immediate stimulus for the sensation is probably tension exerted on the affected membrane by fibrinous adhesions. Since the more distal bronchi and the lung paren-

chyma are known to be entirely devoid of pain nerve endings, the sole source of pain from infarction of the lungs is the involvement of the pleural membranes as described. Pain and the associated chest splinting, together with secretion and hemorrhage into the alveoli, and cough (particularly in extensive infarction), tend to limit vital capacity so as to render breathing difficult, and certainly less effective. Thus dyspnea is a variable manifestation of infarction [113,201,204].

Hemoptysis formerly was regarded as a dominantly important sign of infarction but it is less frequent than was first believed. Nevertheless, the symptom has been reported in 50 and 65 per cent of cases respectively of the entity in two series [32,113]. In another report, bloody sputum was present as the initial symptom in 5 per cent of cases [59]. Hemoptysis is probably associated with the hemorrhage present in necrotic lung parenchyma [21,99,204] and from disruption of the bronchial vessels. The sputum produced shortly after the infarction may be frankly bloody. When the blood is mixed with other secretions it often assumes the "meaty" character so frequently noted in older descriptions. Sputum with dark blood appears during the process of healing.

Cough has been considered one of the less prominent symptoms of lung embolism [73]. However, in a number of reports it was noted in about one-third of cases and was found usually to indicate the establishment of tissue infarction [99,159]. In these cases the symptom apparently results from irritation of the bronchial mucosa (probably within the area of infarction), and from passage of secretions into the normal bronchi. The cough may excite intense paroxysms of pain if a fibrinous pleurisy has com-

Rapid heart action often occurs with pulmonary infarction. In fact, the association of tachycardia, toxicity to ordinary doses of digitalis, and mercurial-fast edema in patients with congestive heart failure has been described as evidence of underlying pulmonary infarction [180]. The factors in the genesis of tachycardia in these instances appear to be similar to the mechanisms which invoke tachycardia following embolism without the occurrence of tissue necrosis.

plicated the disease.

Pulmonary vascular accidents are frequently complicated by *fever* [32,159]. Pyrexia usually occurs when demonstrable infarction or pneumonitis is present. An associated peripheral

phlebitis [204], of course, may incite fever in itself. It commonly comes on abruptly and usually persists for five to seven days. Unexplained fever in a bedfast patient (especially with congestive failure or after surgery) should suggest the possibility of pulmonary infarction. Since the fever is essentially a response to tissue necrosis and inflammation, antibiotic treatment is generally ineffective [32,67,87].

The physical signs of infarction are similar to those of pneumonia or atelectasis. Dullness, diminished breath sounds and rales are often present over the affected regon. In effect, pulmonary consolidation [27,32,201] is the common denominator in these conditions. Evidence of pleural irritation with friction rub may be present [21,159,201]. However, there is frequently a surprising paucity of physical findings even when there are lesions of large size or of disabling symptomatology.

Leukocytosis and elevated erythrocyte sedimentation rates are common [32,123,159,201,204] but these phenomena are so frequently present in other forms of inflammation as to be of limited value

The elevation of serum bilirubin (and the occurrence of jaundice) occasionally observed in pulmonary infarction has been an aspect of interest for many years. It is presumed that the hemolysis of erythrocytes in the hemorrhagic lung infarct is the source of the added bilirubin [100]. Whatever the mechanism, jaundice does not usually appear in these patients unless there has been previous hepatic disease, or unless there is hepatic damage due to congestion, hypoxia or hypotension [32,87,102,113]. Although Wolff [201] reported hyperbilirubinemia in 50 per cent of cases of pulmonary infarction, Chapman [32] found it in only two of twenty cases of the disease. Probably the 10 per cent incidence of jaundice from necrosis of lung tissue is closer to the actual figure. However, a study by Kugel and Lichtman [102] indicated that 94 per cent of cardiac patients with clinical jaundice had outspoken pulmonary infarction.

The serum glutamic oxalacetic transaminase determination, introduced as a test for myocardial infarction, has been applied to experimental pulmonary infarction. The serum level of the enzyme was not found to increase [2]. Nevertheless, Ostrow et al. [137] noted a mild elevation of transaminase levels in eight of fifteen clinical cases of lung infarction. They found that the transaminase values were lower



Fig. 10. Posteroanterior and lateral chest roentgenograms of a patient who was presumed to have pulmonary infarction of the left lower lobe following the sudden onset of chest pain and cough. The film was taken nine days after development of symptoms. The mediastinum is shifted to the left, there is evidence of pleural effusion at the left base with elongated densities in the lung parenchyma. This film is similar to many roentgenograms obtained from patients in whom necropsy examination finally shows the presence of pulmonary infarcts. Some roentgenologists state that the appearance of densities in the lung fields which are contiguous with the pleurae, or are associated with pleural effusion (together with compatible symptomatology), is presumptive evidence of pulmonary infarction.

than with myocardial infarction and that the elevation occurred comparatively late in the course of the pulmonary lesions. The rise of serum transaminase was attributed to lung necrosis, hemolysis or hepatic damage [137].

Radiological Manifestations. Chapman [32] and others consider radiographic examination to be the most reliable means of diagnosis in pulmonary infarction. Chapman was able to confirm the diagnosis by thoracic x-ray study in nineteen of twenty patients. Short [164] demonstrated radiographic evidence of infarction in 111 of 120 patients. (Fig. 10.)

The typical picture begins twelve to twenty-four hours after the embolism. At this time one or more densities of variable size appear in the lower lung fields, in conformity with the usual sites of impaction of the emboli. The densities may be rounded or linear; they are infrequently wedge-shaped or triangular. These radiologic opacities can be compact and highly opaque, or hazy and of indistinct outline so as to be difficult to differentiate from other types of

pulmonary consolidation. Clouding of the costophrenic angles or frank pleural effusion may occur and occasionally obscure the intrapulmonic densities. Elevation of the diaphragm and prominent pulmonary vessels may appear homolateral to the infarct [72,113,164,169,201]. The lung shadows persist for variable periods, and in some cases have been visible for nine weeks after the embolic assault. Usually the x-ray shadows gradually disappear, leaving the lung fields either entirely clear or with a persistent small linear scar to mark the site of the former lesion [164]. The radiological picture of solitary pulmonary cavitation may suggest infarction, since lung abscess may develop during the course of necrosis of the parenchyma [34,101].

# THROMBOEMBOLISM OF SMALL PULMONARY ARTERIES

In recent years there has been increasing interest in embolization due to small or minute thrombi. Towbin [184] noted that 31 per cent

of patients with pumonary embolism at autopsy exhibited occlusions of the tertiary portions of the arterial tree. The conditions under which miliary thrombotic emboli are generated are obscure, except in persons with subacute bacterial endocarditis of the tricuspid or pulmonic valves. Years ago, Möller [126] suggested that pressure in the pulmonary vessels can compress large emboli into the smaller vessels or reduce the embolus to fragments when it strikes valvular bifurcations. Whatever the origin of the thrombotic particles, their impaction in the finer arteries seems to incite physiological responses suggesting pulmonary vascular obstruction. In addition, there has been interest in the question of vascular lesions resulting from minute thromboemboli. Castleman and Bland [29] called attention to the possibility that obstruction of the distal branches of the pulmonary arteries may occur over a long period (eight years in their case) with gradually developing cor pulmonale. They noted also that the patent portions of the arteries, proximal to the emboli, were covered with intimal atherosclerotic plaques. Owen et al. [138] followed up the pathological events occurring in the wake of small and unrecognized arterial occlusions of the lung. Their report included twelve instances of multiple obstructions of the arteries. A number of these patients, observed clinically over a period of weeks, exhibited unremitting congestive heart failure, frequent cyanosis, dyspnea, cough and hemoptysis. The etiologic diagnosis was usually unsuspected during life. Their observations indicated that emboli of small arterial radicles constitute an important cause of subacute cor pulmonale, frequently resulting in death from intractable congestive failure. The emboli of themselves appear to be innocuous and it is not until the multiple obstructions become numerous that right ventricular function deteriorates and circulatory derangements occur.

Other Forms of Miliary Embolization. Another type of miliary pulmonary embolism results from the entrance of amniotic fluid into the maternal venous stream during parturition. The accident [176,177] has usually been observed following complications causing fracture or other damage to the placenta. Amniotic fluid laden with meconium, squamae, lanugo hairs and other debris escapes into the veins through the break in the placenta. Shock, intense cyanosis and death may rapidly follow. Opinion

has been divided as to whether the embolizing particles cause widespread mechanical block of the finer pulmonary vasculature [5,40] or vasoconstriction of the pulmonary arterioles generated by anaphylaxis or intravascular stimuli from impaction of the particles [176,177]. Whether mechanical occlusion or reflexogenic vascular constriction is operative, the ensuing circulatory arrest, acute ventricular dilatation, peripheral venous congestion and sudden death are tell-tale signs of obstruction of the pulmonary circulation. This condition is now recognized as an important factor in current maternal mortality.

Droplets of fat occasionally invade the venous circulation to invoke another form of miliary embolism. Fat embolism has usually been observed following severe trauma or fracture of the long bones [109,161]. Some clinicians believe that fat metabolism has little if any clinical significance [161]; however, other observers [61,109] have noted the precipitate occurrence of shock, cyanosis, cough, hyperpnea, anxiety and coma. The cerebral manifestations have been attributed in part to the anoxia resulting from the embolism. Love and Stryker [109] have stated that there may be striking changes in the size and shape of the fat globules under the force of increased pulmonary arterial pressure, reducing them to a size which permits their escape through the pulmonary capillaries into the systemic circulation. Some of the droplets, finding their way to the cerebral vasculature, produce further circulatory impairment of the brain. These authors studied eighteen patients with particulate fat embolism; ten of these subjects were seriously ill and two died.

A symptomatologic picture similar to that of fat embolism has been reported in instances of massive and rapid air embolism. The quantity of air entering the venous circulation necessary to produce significant vascular obstruction in the lungs is not precisely known; however, the volume sufficient to invoke death from this cause appears to be about 350 cc. introduced rapidly [7,61]. Air embolism is most common in surgical operations of the neck or chest; occasionally it follows diagnostic or therapeutic air injections or intravenous infusions [7]. Therapy must be carried out at once. Patients should be placed in a reclining position with the left side down, and aspiration of air from the right ventricle may be necessary if there is evidence of progressive circulatory occlusion [53].

## RECOGNITION OF PULMONARY EMBOLISM AND INFARCTION

From the experimental and clinical information at hand, it is apparent that a multiplicity of physiologic events is set into operation by pulmonary embolism, and its possible sequel, infarction. Therefore, it is not surprising that the resultant array of symptoms may overlap with those of other cardiac and pulmonary disorders, so that the clinical differentiation often becomes difficult. As a matter of fact, it has been reported that, of cases of pulmonary embolism at autopsy, the correct diagnosis had been made in only 20 to 50 per cent of the patients during life [8,59,65,123,155]. The two diseases for which pulmonary infarction is most frequently mistaken are pneumonia and myocardial infarction [59,123,193,201]. Certain cases of congestive heart failure, and other forms of pulmonary disease (especially atelectasis, pleurisy, pneumothorax, pulmonary neoplasm, and infection such as tuberculosis) are often manifested by very similar symptom complexes [21,32,50,67,159,164]. In addition, primary pulmonary artery thrombosis is occasionally indistinguishable from pulmonary embolism. This uncommon disease process may cause such extensive thrombotic occlusion of the pulmonary arteries as to incite intractable right heart failure with severe dyspnea or to resemble acute massive embolism [9,95,116].

It has been difficult to establish accurate estimates of the mortality rate of patients with thromboembolism of the lung because the clinical diagnosis is frequently obscure. Barker and his associates [12] found a death rate of 38 per cent in a study of 879 cases. Macleod and Grant [113] and Bryne [24] reported a mortality of approximately 20 per cent, the latter study comprising more than 700 instances of embolic accidents to the lungs. Of the patients who died, Byrne noted that 84 per cent succumbed with the first episode. Wolff [201] has emphasized that the likelihood of fatality is increased with succeeding embolic attacks. The immediate cause of death is usually related to acute circulatory collapse or from overwhelming strain and failure of the right ventricle due to pulmonary arterial occlusion [122]. Many patients become comatose preceding death [1]. In patients who survive the acute effects of the embolic process, the general prognosis is related to the underlying disease [112] and particularly to the form and severity of existing heart disease.

#### BRIEF COMMENT ON THERAPY

Because of the anatomical and physiological peculiarities of pulmonary embolism, the principles of therapy must include support of the circulation and the suppression of complications until the embolus and resultant infarct are disposed of in the process of healing. From the data presented, it is evident that in patients with pulmonary embolism (with or without infarction) the diagnosis may be confused with acute myocardial infarction or pneumonia. It is fortunate that the general supportive measures are effectively applicable to any of these conditions until the diagnosis becomes clear. The treatment procedures are well known and will be mentioned briefly to indicate their value.

The fear and discomfort following an embolic assault often respond to the administration of morphine or demerol® [61,67,83,201]. In some instances these drugs produce a surprising relief of distress. The use of oxygen to reduce anoxia, especially in cyanotic patients or in those with vascular collapse, hardly needs comment [21,61,67,83,201,204]. The advent of shock is always an alarming complication requiring prompt treatment with L-norepinephrine [67,173,179]. The use of atropine and papaverine has been advocated to countermand pulmonary vasoconstriction [21,48,61,201]; however, the efficacy of these drugs in the management of this disease has been questioned [67,79]. The administration of theophylline ethylene-diamine (aminophylline) frequently is effective in reducing dyspnea [83,204]. In parallel with this response, aminophylline also has a direct stimulatory action upon the myocardium in producing increased force of systolic contraction [175]. The salutary effects of this drug in heart failure resemble those of digitalis. It is well known that when myocardial failure occurs in consequence of increased pulmonary arterial resistance from lung emboli, the administration of digitalis often will not improve function of the heart [201], but when pulmonary embolism is complicated by heart failure from intrinsic myocardial disease the use of digitalis may be of signal benefit. Under the conditions of pulmonary hypertension from embolism, venesection may be dangerous [48] as the procedure can lead to further reduction of cardiac output.

The administration of antibiotics to prevent

secondary infection of the lungs, especially in the presence of infarction, is advisable [67,83,112].

Many physicians now believe that anticoagulant therapy should be initiated as soon as the diagnosis of pulmonary embolism or infarction has been made, even in the presence of pulmonary hemorrhage. The rationale of anticoagulation rests largely upon the premise that repeated embolism in these patients enhances the probability of fatal outcome [201]. Prompt anticoagulation entails the administration of heparin, after which one of the coumarin drugs may be employed [47,79,83,201].

Embolectomy and stellate block have been performed for recognized large pulmonary

embolism [16,56,73].

Prevention of Thromboembolism. Although venous ligation for the control of repeated embolism from thrombi in the lower extremities has its enthusiastic advocates [24], there are many clinicians who advise the procedure less often than formerly [46,107,123,156,204]. Inferior vena caval ligation is more effective in the prevention of thromboemboli than is femoral ligation [46,156] although the caval ligature is apt to be followed by rather disabling complications of edema, cutaneous ulceration, weakness and pain in the extremities. In fact, these distressing sequelae (in varying severity) have been observed in more than one-half of the cases in which the operation was employed [20,204]. Most physicians administer anticoagulant treatment in patients with outspoken phlebitis or in those with suggestive evidence of pulmonary embolism. Caval ligation then is reserved for the cases in which anticoagulant therapy is contraindicated or in which repeated pulmonary embolism occurs in spite of adequately lowered blood coagulability [20,201].

In general, measures such as early ambulation designed to prevent the formation and dissemination of venous thromboemboli have been disappointing [47,107,147]. Nevertheless, there are few situations in medicine in which sensible treatment, which anticipates thromboembolic accidents, is more necessary than in the bedfast debilitated patient, the postoperative patient, or patients with cardiac disease.

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# Some Metabolic Abnormalities in Liver Disease\*

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THE importance of the liver in the main-I tenance of a normal metabolic pattern can hardly be overestimated. In the absence of this organ, protein is not broken down to serve as a source of energy; the formation of phospholipids and sterol esters ceases; the maintenance of normal body temperature becomes impossible; the blood glucose concentration falls to a low level; and many other metabolic derangements occur so that the organism dies. Fortunately, the mass of liver cells in the human being is so great that a large reserve protects the individual against liver failure until most of the cells have been damaged. If the damage is acute and reversible, the effects are transient and variable. The derangements of metabolism seen in acute hepatitis, for example, are temporary and usually mild; they represent the results of moderate damage to almost all the cells of the liver so that the mass of cells is not greatly diminished. Healing is usually sufficiently complete to prevent the persistence of any of the metabolic abnormalities to be discussed subsequently. For this reason, the present discussion will ignore, for the most part, the derangements observed in acute reversible liver disease, and will focus its attention upon those disturbances which result from destruction of large portions of the organ. Progressive posthepatitis necrosis and Laennec's cirrhosis are examples of the pathological processes which ultimately destroy enough liver tissue to produce serious, relatively irreversible metabolic derangements.

The abnormalities to be discussed are therefore chiefly quantitative (i.e., a result of reduced liver capacity); with few exceptions, the metabolic processes in the diseased liver are qualitatively normal. In these diseases, however, the primary effects of hepatic insufficiency are usually complicated by malnutrition which, in turn, aggravates the degeneration of the liver.

Obstruction to the flow of bile from the liver produces striking alterations in the metabolism of the bile pigments and bile acids; however, since these are discussed elsewhere in this symposium, the abnormalities observed in biliary obstruction will be discussed only in relation to other metabolic disorders.

Claude Bernard's observation that the liver releases glucose into the blood was the first important hint of the physiological function of the liver. Since this discovery, the role of the liver in stabilizing the blood glucose has been emphasized repeatedly. When the blood glucose is elevated, the liver (along with other tissues) takes up glucose. The capacity of the splanchnic system (liver, spleen and gastrointestinal tract) to trap glucose is normally sufficient to dispose of large glucose loads [1,2]. The peak glucose uptake by the splanchnic system is usually more than enough to account for the total rate of glucose disappearance from the blood. (Table 1.) This does not mean to imply that most of the glucose removed from the blood goes to the splanchnic system, since it is well recognized that a large part of this glucose enters other organs as well as the muscle and fat cells of the periphery. The splanchnic "peak uptake" is probably sustained for only a brief period.

The glucose trapped by the liver enters a variety of reactions which result in its storage as glycogen, or its dissimulation via either anaerobic (Meyerhoff-Embden) or aerobic pathways. In the course of its oxidative metabolism, glucose gives rise to pentoses [3] and, indirectly, to a variety of important compounds such as purines [4]. An important by-product of the oxidation of glucose-6-phosphate to 6-phosphogluconic acid

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is the production of the reduced form of triphosphopyridine nucleotide (TPN·H). A different type of oxidation results in the formation of glucuronic acid [5] for conjugation with a variety of substances prior to their urinary excretion. These relationships are presented schematically in Figure 1.

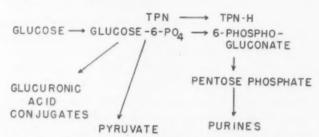


Fig. 1. Some of the pathways of glucose metabolism in the liver. (Many intermediate steps have been omitted.)

A large part of the glucose taken up by the liver is converted to fatty acids. This conversion depends on the continuing presence of an active glucose breakdown system. The reason for this dependence is not altogether clear, but it may reflect the need for oxidative processes elsewhere to provide TPN·H needed for the reduction of glucose to fatty acids [6].

Table 1
REMOVAL OF GLUCOSE BY THE SPLANCHNIC SYSTEM IN MAN

Arterial Glucose Concentration (mg./100 ml.)	Splanchnic Glu- cose Uptake (mg./kg./min.)*	Calculated Glu- cose Disposal Rate (mg./kg./min.)†
270	7.8	3.3
304	6.9	3.7
369	5.9	4.5
445	10.7	5.3

<sup>\*</sup> Calculated by multiplying the arteriohepatic venous glucose difference by the estimated hepatic blood flow [2].

The maintenance of a normal blood glucose level during fasting requires constant addition of glucose to the blood to replace that which is withdrawn by the peripheral tissues for their use. Although small amounts of glucose can be secreted into the blood by the kidney [7], the amount thus released is negligible. Other peripheral tissues are unable to release glucose because they lack the enzyme glucose-6-phosphatase.

Consequently, the major burden of maintaining the blood glucose at a normal concentration during fasting falls on the liver. Since ingested carbohydrate is normally completely cleared from the blood within two hours after a meal, the liver may secrete glucose into the blood for as much as eighteen hours a day. This glucose is

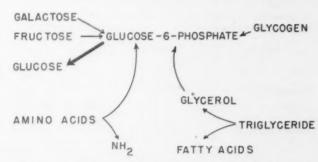


Fig. 2. Sources of glucose in the liver. (In the interest of simplicity many intermediate steps have been omitted, and the reversible reactions are not so indicated.)

derived in part from ingested glucose, which has been stored as glycogen, in part from other hexoses which have been converted to glycogen, and in part from other glucose precursors such as amino acids, pentoses and glycerol which may be converted to glucose by the interchanges of the anaerobic and aerobic glycolytic pathways. (Fig. 2.) Since the quantity of glycogen stored in the normal postprandial human liver is probably not more than 4 per cent of the weight of the organ [8,9], only about 75 gm. of glycogen is available for maintenance of the blood sugar level during fasting. The rate of glucose secretion, which is similar in the various fasting mammals studied to date, approximates 3 mg./kg./ minute or 12 gm./hour for a man weighing 70 kg. If one can assume that this rate is constant during the night, the quantity of glycogen stored in the liver is obviously not sufficient to supply the amount of glucose required during the twelve hours or more of nightly fasting. Thus the conversion of amino acids and other precursors to glucose is a necessary step in the maintenance of normal blood glucose concentration by the liver. If the processing of glucose precursors is seriously delayed, it may be difficult to maintain a normal blood sugar concentration.

In liver disease, maintenance of the normal blood glucose concentration may be impaired because of a reduction in the glycogen stores and in the rate at which glucose precursors can be metabolized. The fact that the bulk of glycogen

<sup>†</sup> Calculated by assuming the removal of 4 per cent of the arterial glucose per minute, and the distribution of glucose equally throughout the extracellular water.

in the cirrhotic liver is reduced has been demonstrated repeatedly by tests of the ability of the liver to raise the blood glucose concentration after the administration of glycogenolytic substances such as epinephrine [10-13] or glucagon [14,15]. The tests can be made more elegant by

TABLE II GLUCOSE TOLERANCE IN CIRRHOSIS OF THE LIVER\*

Author	Normal	Cirrhosis
Danowski [15]	12.2 ± 2	9.6 ± 2 mg./kg./ minute cleared
Amatuzio [75]	3.7 ± 0.5	from blood 2.2 ± 0.8 per cent of capillary blood glucose fall
Campbell [76]	Below 110 mg. % at 120 minutes	per minute 3/25 elevated

<sup>\*</sup> All tests were performed after the injection of a glucose load intravenously.

measuring the appearance of glucose in the hepatic venous blood, obtained by catheterization [16]. Similar results have been obtained by depleting the liver glycogen by starving phlorhizinized human subjects [17]. In all these experiments, cirrhotic livers have released less glucose than normal livers. The defect is probably a result of a reduced mass of cells rather than a reduced glycogen concentration in each cell, since the concentration of glycogen in liver biopsy specimens from cirrhotic subjects has been found not to be significantly less than in normal subjects [18], when the glycogen is estimated densitometrically from stained histological preparations and areas of fibrosis are excluded [9].

Hexoses other than glucose are rapidly converted to glycogen or glucose-6-phosphate in the normal liver. (Fig. 2.) As a result, galactose and fructose can usually be used as nutritional substitutes for glucose. In cirrhosis, however, galactose is metabolized more slowly than normal [19] and the disappearance of fructose from the blood may be somewhat delayed [20]. The delayed conversion of galactose by the liver has been recognized for many years, and is the basis of the galactose tolerance test for liver dysfunction.

Since the glycogen reserves are reduced in cirrhosis, there is an increased dependence on

gluconeogenesis. This implies an increase in the rate of protein breakdown which will be discussed in detail subsequently.

In view of these considerations, one might expect that hypoglycemia would be an important problem in patients with liver disease. In patients with certain types of hepatic carcinoma it may indeed be a frequent complication [21]. The fact that it is actually rather a rare finding in cirrhosis [22] attests in part to the reserve power of the liver; but it may also reflect other factors. It has been suggested that the liver may in some way accelerate the utilization of glucose in the periphery [23]. Schwartz has recently isolated and partially purified a material from the liver which increases the rate at which glucose leaves the blood and enters the peripheral tissues [24]. The demands for glucose secretion by the cirrhotic liver may, therefore, be less than those by the normal liver. In support of this interpretation is Myers' observation [25] that the rate of glucose secretion in fasting cirrhotic patients was less than in normal control subjects, although the arterial glucose concentrations were the same. Moreover, patients with liver failure are often anorectic, so that their carbohydrate metabolism has some of the features of "starvation diabetes."

Although spontaneous hypoglycemia is rare in liver failure, one might expect to find a reduced glucose tolerance because of the factors tending to reduce peripheral glucose utilization just mentioned, combined with the reduced ability of the failing liver to trap carbohydrate. Abnormalities of the glucose tolerance test have frequently been described in patients with liver disease, but evaluation of these changes depends on the type of test used. Oral glucose loads are deceptive because they fail to take into account abnormalities of absorption which may occur in this disease. When the glucose load is given intravenously, a considerable portion of patients clear the glucose from their blood more slowly than normal. (Table II.) The degree of hyperglycemia thus produced rarely is high enough to produce glycosuria and the other metabolic abnormalities characteristic of diabetes are absent. The fasting blood glucose concentration is not elevated.

The quantitative importance of the phosphogluconate oxidative pathway [3] in carbohydrate metabolism in the normal human liver is not entirely certain. Various estimates of the fraction of glucose which is dissimulated

via this series of reactions in the livers of experimental animals vary from less than 10 to over 50 per cent [26-29]. No direct quantitative observations have as yet been made in human beings. It seems likely, however, that the pathway is active in human tissues [20,30] and that it may become deranged in liver disease [15,19]. It is possible that a variety of disturbances common in severe liver disease may be traced to abnormalities of this series of reactions. For example, the reduction of the double bond between carbons 4 and 5 in the corticosteroid nucleus, which is slowed in patients with liver disease [31,32], depends on the presence of adequate amounts of TPN·H [33] which, as has previously been mentioned, is produced by the oxidation of glucose-6-phosphate to 6-phosphogluconate (Fig. 1), as well as by other reactions. The defective synthesis of fatty acids in liver disease may also depend in part on the absence of adequate TPN·H [6]. The production of pentose as a precursor of pentose nucleic acids probably depends on this pathway; moreover, ribose-5-phosphate, one of the intermediates in the sequence of changes, is a component of the first step in the synthesis of purines [4]. The clinical importance of these observations remains to be determined; but the possibility that certain of the refractory macrocytic anemias of hepatic failure may reflect these relationships seems worth further consideration.

When a glucose load is given to a normal person, the quantity of certain intermediate derivatives in the plasma increases. Among the substances thus increased are pyruvic, lactic and alpha-ketoglutaric acids. In patients with liver failure, the rise of these substances after carbohydrate administration is exaggerated [34–38]. The cause of this increased response is not clear, but one possible explanation is that the injection of glucose increases the quantity of intermediates passing down the anaerobic glycolytic pathway into the tricarboxylic acid cycle to such an extent that it exceeds the capacity of this system, thus permitting some of the overload to spill out into the plasma.

As has previously been mentioned, amino acids are continuously deaminated to serve as sources of energy. The chief organ concerned in this process is the liver; indeed, in animals after experimental hepatectomy the constant normal breakdown of tissue proteins causes a progressive rise of plasma amino acids. In very severe liver failure, the plasma alpha-amino nitrogen concentration may therefore be elevated and free amino

acids may appear in the urine in increased quantities [39].

The pathways by which amino acids are normally deaminated are shown in Figure 3. The final common pathway by which the liver disposes of amino nitrogen is by way of glutamic

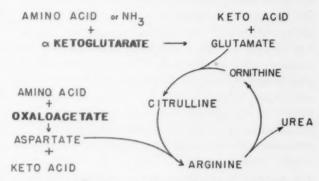


Fig. 3. Pathways by which amino acids are deaminated and urea formed in the liver. The compounds in heavy type are intermediates in the tricarboxylic acid cycle. The reversible nature of the transamination reactions has not been indicated.

acid and the formation of urea. If the capacity of this system is diminished, some of the amino nitrogen enters the blood as ammonium ion rather than as urea. Moreover, the continuing presence of excess ammonium might be expected to reduce the rate at which glutamic acid is deaminated, thus reducing the quantity of alpha-ketoglutarate available for the functioning of the tricarboxylic acid cycle [40]. Since the integrity of this cycle is necessary for the functioning of the urea synthesis mechanism [41] the defect would tend to perpetuate itself.

Although a considerable portion of the ammonium load arises from hepatic deamination reactions, a significant amount of extrahepatic ammonium production occurs as a result of gastrointestinal bacterial activity [42]. Ordinarily this ammonium is carried to the liver in the portal vein and there it is completely trapped, but when the liver's ability to convert ammonium to urea is impaired, or when collateral circulatory changes permit intestinal venous blood to enter the systemic circulation without passing through the liver, the additional burden of ammonia of intestinal origin may cause a rise in the plasma ammonium concentration. With this thought in mind, the use of antibiotics to inhibit intestinal bacterial growth has been suggested [38,43,44] as a way of treating patients with symptoms attributed to ammonia toxicity.

These theoretical considerations find clinical expression in certain serious derangements of the protein metabolism of patients with liver failure, who may tolerate nitrogen-containing foods poorly. A high protein-diet may precipitate increasing lethargy, neurological disturbances and ultimately coma [45,46]. In such patients, the volatile base content of alkalinized plasma is often increased, a finding which is usually interpreted as an indication that the plasma ammonium is elevated. The mechanism by which the elevation of blood "ammonium" is associated with neurological deterioration is not clear. Some are of the opinion [47] that the ammonium itself is toxic; others suggest that the abnormalities of alpha-ketoglutarate and glutamic acid metabolism which are reflected in the plasma ammonium are the cause [48]. The fact that correlation between plasma ammonium and the level of consciousness is not always good has suggested to some that there may be only a very indirect connection between the two [38]. One possible explanation for this discrepancy may lie in the suggestion that it is not the ammonium ion but the free ammonia which is toxic. Ammonium dissociates to ammonia in the following manner:

$$NH_4^+ + OH^- = NH_2 + HOH$$

so that any increase in the concentration of OH-(or rise of pH) will tend to drive the equilibrium to the right and increase the ammonia concentration [49]. Since alkalosis is not uncommon in liver failure [50], measurement of "ammonium" alone may not give enough data to make possible a correlation between the meaningful fraction of ammonium and the degree of neurological impairment.

Numerous attempts have been made to correct the defect in amino acid metabolism. Of these, the administration of glutamic acid (to trap excess ammonium as glutamine) [51–53] has had the widest trial. The use of arginine, to "prime" the urea synthetic mechanism, has also been suggested since this amino acid prevents the acute rise of plasma ammonium which follows the intravenous injection of mixed amino acids [54–56]. It is still questionable whether or not these maneuvers actually improve the prognosis of the patients.

When the plasma ammonium concentration is elevated, this substance is removed from the plasma by many of the peripheral tissues, in-

cluding the brain. This fact has suggested that the primary difficulty in cerebral metabolism may be a deficiency in the brain of alpha-keto-glutarate which is decreased by reacting with ammonia to form glutamic acid [40,48]. This would be expected to inhibit the activity of the Krebs tricarboxylic acid cycle and thus reduce the energy available for the normal activity of the brain.

In liver failure, anabolism of proteins is disturbed as well as catabolism. Most patients with serious hepatic derangement have a history of anorexia and partial undernutrition. In some instances (for example, in alcoholic subjects) this malnutrition may be of long duration. Consequently, the raw materials for protein synthesis may be available only in limited quantities. Even minor abnormalities of liver function, moreover, are manifested by abnormal protein synthesis. Tests of altered plasma protein patterns such as the thymol turbidity or cephalin flocculation tests rely on these abnormalities to indicate the presence of abnormal liver function. When the functional derangement is severe, the pattern of plasma proteins may be so distorted that it becomes obvious on examination by one of the protein fractionating procedures such as paper electrophoresis [57]. The most obvious and striking change usually is a reduction in plasma albumin. Globulins are often increased, and the pattern of increase is not uniform, so that the distribution of proteins in the various categories may become bizarre. The concentrations of certain specific proteins such as ceruloplasmin [58] and zinc-protein enzymes [59] are also altered. Estimates of plasma protein synthesis in liver disease have led to the conclusion that the turnover of the various proteins is altered in patients with cirrhosis [60].

The physician treating a patient with liver failure must recognize the contradictory problems raised by intolerance for proteins and the need for protein re-alimentation. Fortunately, only in the last stages of liver failure is the tolerance for proteins so small that reasonably adequate quantities of this nutriment cannot be tolerated. When adequate amounts of protein are given together with sufficient non-protein calories to "spare" the dietary protein from immediate deamination, many of the disabilities of hepatic failure may be reversed. The hypoproteinemia, ascites and edema may improve, the blood vessels and other tissues may become less fragile, and the patient's sense of well-being

may return. In association with these changes, biochemical improvements may also become manifest: the plasma protein pattern may return toward normal; the tolerance for amino acids and for glucose may improve; and the deranged intermediary metabolism of a variety of substances such as galactose, bile acids and pigments, and various hormones including the steroids and thyroxine may return toward normal. The salutary effects of high protein feeding have been emphasized by Patek et al. [61].

The liver plays a major part in the synthesis and transport of lipids. Triglycerides, for example, are carried in the plasma chiefly in the form of lipoproteins. These substances appear to be synthesized, in part at least, in the liver. In patients with liver failure associated with biliary cirrhosis the pattern of lipoproteins in the plasma is altered [62,63]. Part of the plasma triglycerides are normally broken down to unesterified fatty acids, which promptly attach themselves to albumin. In the absence of adequate supplies of this protein the ability of the body to clear triglycerides from the blood [64] may be reduced. As a consequence, these substances may accumulate in the plasma in excessive quantities after a meal high in fat. If enough triglycerides appear in the plasma, they form aggregates large enough to scatter light and produce a milky appearance in the plasma [65]. Since a low plasma albumin concentration often occurs in liver failure, one might expect the plasma to become lactescent after a meal high in fat. If the patient eats sparingly, however, lactescence may not be seen; and in most patients with advanced liver failure anorexia prevents ingestion of enough fat to produce milky plasma.

Phospholipids are also produced and destroyed chiefly in the liver [66,67]. In liver failure, therefore, the quantity of these materials in the plasma is usually reduced. Cholesterol also is formed in the liver and the sterol thus formed passes freely into the plasma [68]. The failing liver synthesizes less cholesterol than normal. As a result, there is often a reduction of both plasma cholesterol and phospholipid concentration although the ratio of non-esterified cholesterol to phospholipid usually remains normal [69]. Under normal conditions, the liver esterifies cholesterol with fatty acids (chiefly linoleic and oleic acids) [70]; this function is reduced early in liver failure so that the portion of the total plasma cholesterol which is esterified falls [69]. The combination of low cholesterol

with a high unesterified fraction is, therefore, characteristic of liver failure [69].

A considerable portion of the cholesterol in the plasma is ultimately secreted into the bile, together with the chief degradation product of cholesterol, the bile acids [71]. When biliary obstruction occurs, this secretion cannot occur at a normal rate, and consequently, the plasma cholesterol and bile acid concentrations rise. The rise in bile acids may aggravate the hyperlipemia [72]. This rise is maintained as long as the ability of the hepatic cells to synthesize and metabolize cholesterol continues unimpaired. If the liver parenchyma suffers from the results of long-standing biliary obstruction, the pattern may be blurred by the superimposed reduction of cholesterol synthesis resulting from hepatocellular damage.

In addition to its central role in the metabolism of carbohydrate, protein and fat, the liver plays an important part in the normal metabolism of many other substances. Space does not permit a complete rehearsal of the derangements which occur in these functions when the liver fails, but a few may be mentioned. The importance of the liver in the reduction of adrenocorticoids has already been mentioned; similar important modifications take place in the structure of other steroids, including the androgens, estrogens and progestins. Among the amino acids which are catabolized in the liver, the thyroid hormones are especially interesting for they, like the steroids, are partially inactivated in the liver and also are conjugated there to forms suitable for biliary excretion [73]. Conjugation, especially with glycine, sulfate and glucuronic acid, is an important method for disposal of sparingly soluble materials. The steroids, bile acids and certain aromatic compounds used as pharmaceuticals are among the materials the excretion of which depends on the ability of the liver to form soluble conjugates; indeed, the ability of the liver to conjugate benzoic acid with glycine to form hippuric acid has long been used as a test of liver function. The gynecomastia and testicular atrophy of liver failure have been blamed on the failure of the liver to inactivate estrogens normally. The pigmentation of the skin sometimes seen in patients with liver failure may reflect the fact that the melanocytestimulating hormone of the pituitary normally is destroyed in the liver [74].

The metabolic abnormalities occurring in liver failure touch on every aspect of human

physiology. This review can give only a rough indication of the complexity of the interrelated problems arising from these disturbances.

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# Clinico-pathologic Conference

# Rapidly Progressive Pulmonary Infiltration, Fever and Coma

S TENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. H., a fifty-four year old white male farmer, was transferred to the Barnes Hospital on February 15, 1957. He died on March 3, 1957. The presenting problems were fever, cough, weight loss and malaise of six weeks' duration and, more recently, confusion and disorientation. The anamnesis obtained from the family was incomplete. The patient had consumed large amounts of alcoholic beverages for over twenty-five years; this habit had interfered with his vocational and family life. A vague history of weight loss, fatigue and melena during the year preceding admission was given by the patient. Six weeks prior to admission to Barnes Hospital he saw his physician and was hospitalized elsewhere. His complaints were sore throat, cough and fever. His daily temperature ranged between 101° and 103°F. The hemoglobin and red blood cell count were normal. The white blood cell count was 11,000 cells per cu. mm. with a "left shift." Toxic granulations were noted in the polymorphonuclear leukocytes. Urinalysis revealed 2 plus proteínuria. A roentgenogram of the chest taken on January 22, 1957 (Fig. 1) showed bilateral hilar masses and a nodular infiltrate in both lung fields. Ten days later a repeat film of the chest showed an extension of the infiltrate. Sputum cultures grew out gram-positive cocci, sensitive to the broad spectrum antibiotics. A biopsy specimen of a right femoral lymph node was obtained three days prior to transfer and was interpreted as "malignant tumor, type and origin undetermined." Antibiotics were administered to the patient during his hospitalization. There was no history of previous illness or hospitalization.

Physical examination at the time of his admis-

sion to Barnes Hospital revealed the following: temperature, 38.6°c.; pulse, 110, regular; respirations, 18 to 24; and blood pressure, 120/80 mm. Hg. The patient was disoriented and thrashed about aimlessly. Although obese, signs of weight loss, dehydration and chronic illness, including a Hippocratic facies were present. The skin and the optic fundi appeared normal. The tongue appeared red and dry with flat papillae. The gingivae were red and bleeding. The pharynx was covered with thick yellow exudate. The neck was supple. A firm, tender, fixed lymph node, 1 cm. in diameter was present in the left femoral area. The recent incision in the right femoral area was red and swollen. The lungs expanded poorly with respiration. An increase in tactile fremitus and breath sounds, and moist, crackling rales were present over the lower one half of both lung fields posteriorly. The heart was enlarged to the left by percussion but was otherwise normal. The abdomen was distended, tympanitic and tender to palpation. There was no fluid wave or shifting dullness. The liver edge was palpable 8 to 9 cm. below the right costal margin, being firm and tender. A mass in the left upper quadrant of the abdomen was palpated by one observer. Examination of the rectum and genitalia was normal. The nail beds appeared slightly cyanotic. Clubbing was not present. There was no edema. Neurological examination was normal.

The laboratory data were as follows: hemoglobin, 14.6 gm./100 ml.; white blood cell count, 11, 150/cu. mm. with 24 per cent band forms, 69 per cent polymorphonuclear leukocytes and 7 per cent lymphocytes. The urine specific gravity was 1.025; there was a trace of protein; 0 to 2 white blood cells per high power field were

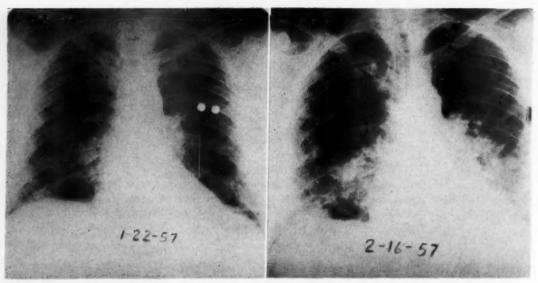


Fig. 1. Patient W. H. Roentgenograms of the chest taken on January 22, 1957, and on February 16, 1957.

present in the centrifuged sediment. The stool was positive to the guaiac test. The cardiolipin reaction was negative. Non-protein nitrogen was 38 mg./100 ml. at the time of admission but was 16 mg./100 ml. seven days later. Fasting blood sugar was 100 mg./100 ml. The serum sodium was 133.5 mEq./L. The serum CO<sub>2</sub> combining power, chloride and potassium were normal. The total serum proteins were 5.0 gm./100 ml. with both albumin globulin 2.5 gm. per cent. The acid phosphatase was 2.2 King-Armstrong units. The alkaline phosphatase was 6.0 Bodansky units. The prothrombin level was 45 per cent of normal. There was a decrease of two seconds in the prothrombin time after the administration of vitamin K-1 oxide intravenously. The cephalin cholesterol flocculation test was 3 plus. The thymol turbidity test was 1.8 units. Serum cholesterol was 118 mg./100 ml. Bromsulfalein retention was 25 per cent after forty-five minutes. An electrocardiogram revealed an abnormal form of ventricular complex compatible with left ventricular strain and sinus tachycardia. Roentgenographic examination of the chest (Fig. 1) revealed multiple, round, nodular areas of infiltration throughout both lung fields thought to be compatible with diffuse metastatic lesions. There was a suggestion of lymphangitic spread of tumor. Left ventricular enlargement was evident. The radiologist suggested renal carcinoma as a possible primary site. Roentgenographic examination of the abdomen was indeterminate for the presence of retroperitoneal tumor. No evidence of bone destruction was seen. Roentgenographic examination

of the skull failed to demonstrate evidence of metastases to the cranial vault. Lumbar puncture revealed normal pressures and clear fluid. Cerebrospinal fluid protein was 32 mg./100 ml., sugar was 117 mg./100 ml., and the chloride was 58 mEq./L. Neisserian organisms and a heavy growth of white staphylococci were cultured from the throat. No pathogens could be isolated from the feces, cultured at the time of admission. Four blood cultures as well as a urine culture were negative.

The patient remained confused and disoriented throughout the sixteen days of hospitalization. His fever ranged from 38°c. to slightly over 40°c. He was treated with fluids intravenously and with oxygen. Antibiotics were administered in large doses. He received penicillin for the first 11 days of hospitalization and streptomycin for the first eight days. During the last thirteen days of hospitalization, erythromycin was administered intramuscularly; during the last ten days chloramphenicol was also given intramuscularly. The biopsy specimen obtained prior to transfer to Barnes Hospital was reviewed by the surgical pathologist who could not make a diagnosis of malignant neoplasm nor of any other specific pathological process. On the seventh hospital day the enlarged left femoral lymph node was excised and the liver was biopsied. The bone marrow was aspirated for cytological and cultural studies. The liver biopsy revealed fatty metamorphosis and portal fibrosis. No diagnosis could be made on the lymph node biopsy or on the bone marrow aspiration, and the cultures of both

were sterile. On the seventh hospital day, a protracted diarrhea developed. Culture of the stool revealed a heavy growth of a coagulase-negative white staphylococcus. At this time the white blood cell count was 4,800 per cu. mm. with 28 per cent stabs, 58 per cent polymorphonuclear leukocytes and 14 per cent lymphocytes. The serum calcium was 7.4 mg./100 ml. and the serum phosphorus was 1.5 mg./100 ml. The hemoglobin level had fallen to 9.9 gm./ 100 ml.

A repeat chest roentgenogram was obtained at the patient's bedside on the thirteenth hospital day. There appeared to have been an interval increase in the multiple discrete radiodensities previously described. Because of the patient's failure to respond to antibiotic therapy and the probable diagnosis of malignant disease, 18 mg. of nitrogen mustard were administered intravenously on the thirteenth hospital day. On the fifteenth hospital day, ascites was noted and an abdominal paracentesis was performed. Five hundred ml. of straw colored fluid which clotted after standing was obtained. This fluid was a transudate with 1,000 red blood cells and 208 white blood cells per cu. mm. The fluid was sterile; a cell block revealed fibrin, mesothelial cells and lymphocytes with no evidence of tumor cells. On this day agglutination tests for salmonella were negative. Agglutination reactions for brucella were 2 plus in a dilution of 1 to 320 and negative in higher dilutions. The patient continued to have fever and shaking chills, and on the sixteenth hospital day the abdomen was noted to be more distended and tender. Easy bruisability was also noted. The hemoglobin was 9.6 gm./100 ml., the white blood cell count was 1,700/cu. mm. and the platelet count was 303,000. The differential showed 8 per cent band forms, 86 per cent polymorphonuclear leukocytes, 2 per cent lymphocytes and 4 per cent monocytes. The patient's respirations became irregular, slow and shallow. He remained comatose and died on the seventeenth hospital day.

### CLINICAL DISCUSSION

DR. EDWARD REINHARD: This patient was a fifty-four year old farmer whose history had to be obtained largely from his family and is of questionable reliability. He had a vague history of weight loss, fatigue and melena during a period of one year. He had malaise, sore throat, cough and fever for only six weeks. The physical

findings revealed a spiking temperature with a proportionately elevated pulse rate. He was disoriented and thrashing about aimlessly. He had a hippocratic facies. He was dehydrated. The gums were red and bleeding. There was a thick yellow pharyngeal exudate. There was a 1 cm. left femoral node and an inflammatory reaction at the site of the right femoral biopsy. He had increased breath sounds and moist rales in both lower lung fields. The liver edge extended 9 cm. below the right costal margin and was tender. One observer described a mass in the left upper quadrant of the abdomen which he thought was spleen. Laboratory abnormalities included a leukocytosis with a shift to the left, a trace of proteinuria and a guaiac positive stool. The non-protein nitrogen was initially 58 mg. per cent but when his dehydration was corrected this value declined. Some evidence of hepatic functional impairment was present in that the serum albumin was 2.5 gm. per cent; the prothrombin level was 45 per cent of normal; the cephalin cholesterol flocculation was 3 plus; and bromsulfalein retention was 25 per cent at forty-five minutes. The spinal fluid findings were normal. In addition to these data, only two positive cultures were obtained. A heavy growth of staphylococcus albus from a throat culture and a similar coagulase-negative organism from the stool. Blood and marrow cultures were negative. Dr. Humphrey, will you review the roentgenograms?

DR. WILLIAM HUMPHREY: We have two examinations of the chest previous to the Barnes Hospital admission. The first, which was obtained about three weeks after the onset of symptoms, indicated moderately pronounced hilar adenopathy with bilateral basilar infiltration. On a subsequent examination two weeks later, a slight increase in the hilar adenopathy and the pulmonary infiltration was seen. The roentgenograms taken on admission here, showed further increase in the adenopathy and in the distribution and extent of the infiltrates, all lungs appeared to be involved. In some of the densities, there appeared to be central destruction indicating the presence of small cavities which might have been abscesses. The evolution of the disease appeared too rapid for neoplastic disease with but two exceptions which seem very unlikely; (1) chorionepithelial cell carcinoma metastasis will sometimes be very rapid in evolution, and (2) alveolar carcinoma of the lung might present a picture

somewhat like this. We did note some calcification apparently in a primary complex. A film of the abdomen showed no obvious abnormality. On the last film of the chest there appeared to be further progression of the infiltration and adenopathy. The most likely diagnosis is pulmonary mycosis. There is no way of differentiating with certainty between what would appear to be the acute form of primary nocardiosis, aspergillosis, cryptococcosis, histoplasmosis, and actinomycosis.

DR. REINHARD: Dr. Spjut will you discuss the

biopsy material?

DR. HARLAN SPIUT: The slide of the femoral node obtained from Illinois showed some obliteration of the nodal architecture, although the sinusoids were still present and there appeared to be an increased cellularity of the lymph node. Under a higher power, most of the cells that formed this peculiar cellularity, appeared to be histiocytes. There was nothing to suggest that this was a malignant neoplasm, although at first glance, one would consider, perhaps lymphoma. These cells seemed to fill the sinusoids. We did see evidence of phagocytosis in these cells suggesting that they were true histiocytes. There was no evidence of granuloma formation, necrosis or organisms such as histoplasmosis. We were unable to make a specific diagnosis. This tremendous histiocytic response suggests however that a histiocytosis or reticuloendotheliosis should be considered. The femoral node that was removed while the patient was in Barnes Hospital was quite cellular but again no specific diagnosis could be made. There were a fair number of histiocytes but fewer than in the node removed previously. The bone marrow sections showed maturing granulocytes and a normal distribution of cells with perhaps some slight shift to immaturity. No specific diagnosis could be made.

DR. REINHARD: In contrast to Dr. Humphrey's interpretation of the chest film, the official report in the hospital chart mentioned that the most likely diagnosis was lymphangitic spread of carcinoma. I have discussed these films with other people in the Department of Radiology and at least one person still believes that this was the best diagnosis on the basis of the films alone. Dr. Goldman, do you have any comments on bronchogenic carcinoma as a possibility in this case?

DR. AL GOLDMAN: Both the extensiveness of the pulmonary process as well as the rapidity of spread make the diagnosis of bronchogenic carcinoma unlikely. The roentgenographic findings would be compatible with alveolar cell carcinoma. However, again the rapidity of progression would be against this diagnosis.

DR. REINHARD: The diagnosis of a malignant lymphoma was entertained and four days prior to death, at a time when the patient was febrile, he was given a course of nitrogen mustard therapy without any apparent benefit and with no significant effect on his febrile course. Actually in the last four days, his fever, if anything, was higher than it had been prior to the nitrogen mustard therapy. Dr. Harrington, do you think we have to consider a malignant lymphoma and if so, what type would be most likely?

DR. WILLIAM HARRINGTON: I must say, I did not seriously consider it, although I suppose it is a possibility. If you had to reconcile the findings with this course, it would probably be a Hodgkins sarcoma or reticulum cell sarcoma.

DR. REINHARD: Dr. Moore, do you think the failure of the fever to respond within this period of time constitutes evidence against Hodgkin's disease?

DR. C. V. Moore: In the majority of cases of Hodgkin's disease, one would see evidence of a decline in the temperature curve by the end of four days but there are numerous instances in which it takes from six to eight and even ten days before the temperature does respond to the administration of nitrogen mustard.

Dr. Reinhard: Let us now consider possible infectious etiologies for this patient's pulmonary disease. Multiple cultures for microorganisms were taken: four blood cultures, a urine culture, a stool culture on admission and a bone marrow culture all of which were negative. A lymph node culture revealed a few colonies of staphylococcus albus. These were thought to be contaminant organisms. Only two cultures were positive. From the pharyngeal exudate, a very heavy growth of Staphylococcus albus was obtained. A stool culture taken about eight days after admission at a time when the patient was receiving intensive antibiotic therapy and was suffering from diarrhea showed a heavy growth of coagulase-negative Staph. albus. Dr. Beeson, are these results of any great significance?

Dr. Paul Beeson: I would think the cultures probably represent a complication of the intensive antibiotic therapy.

Dr. Reinhard: The brucella agglutinins were

4 plus up to a dilution of 1 to 60 and 2 plus at a dilution of 1 to 320. The patient was a farmer. Dr. Harford, is it conceivable that brucellosis could account for this clinical picture and course?

DR. CARL HARFORD: Brucella pneumonia has been described. I think it is unlikely in this case, chiefly because the therapy received should have controlled the fever. Also, in active brucella infection there is usually a considerably higher titer of agglutinins.

DR. REINHARD: How many healthy farmers would have a titer approaching 320?

DR. HARFORD: I would have to guess but I would think quite a few.

DR. REINHARD: If this patient's acute febrile illness was due to a specific infection, and the infecting organism was not controlled by massive doses of penicillin, streptomycin, tetracycline or chloramphenicol, one would have to postulate the presence of a resistant organism. For this reason fungi would have to be considered prominently among the possibilities. Dr. Magee, would you review the studies that you and Dr. John Keye did concerning the increase in fungal infections at Barnes Hospital in recent years?

DR. EDWIN MAGEE: Of eighty-eight cases of fungal infection that came to autopsy at Barnes Hospital from 1919 to 1955, forty occurred in association with another or primary disease. The primary diagnosis in twenty-one patients was leukemia or lymphoma. Since 1947 we noted a precipitous rise in the incidence of fungal infections among patients with leukemia and lymphoma; whereas there was no significant change in the incidence among patients with other diseases. In fact, during the last year of our study, 20 per cent of the patients who came to autopsy with leukemia and lymphoma had a significant fungal infection. It is of interest that actinomycosis, blastomycosis and coccidiomycosis occurred only as primary infections, and candidiasis and aspergillosis occurred only as complicating infections. Histoplasmosis, cryptococcosis and mucormycosis occurred as both primary and secondary infections. Of the forty patients with secondary fungal infections, 75 per cent received antibiotics for seven days or longer, 30 per cent received cortisone for seven days or longer, 35 per cent received antileukemic agents, and 35 per cent received roentgen therapy. Most of the patients with leukemia or lymphoma received two or more of these therapeutic agents. It is our impression that the

therapy employed in the treatment of the underlying disease played a major role in the development of the secondary fungal infection.

DR. REINHARD: In the patient under discussion today, we have good evidence that he had his primary pulmonary disease, whatever it was, first, and then received intensive antibiotic therapy. It is difficult therefore to consider the antibiotics as an explanation for the development of a disseminated fungal infection, although they could have aggravated such an infection. Dr. Beeson, what do you think about the possibility of a fungal infection in this case, with or without an associated lymphoma or some other disease?

DR. BEESON: A fungal infection is certainly a possibility. I think that if he had blastomycosis, one would have expected a response to some of the antibiotic therapy. However, the absence of any fungus in the cultures seems to be a strong point againt this over-all diagnosis.

DR. REINHARD: We did not have any sputum cultures. The patient was not raising any sputum. Would you like to mention any other fungal infections that could produce this picture in the lungs?

DR. BEESON: Blastomycosis and moniliasis.

DR. REINHARD: Dr. Goldman, you have seen a great many fungal infections of the lungs. What specific infection might produce multiple round nodular lesions such as we see here?

DR. GOLDMAN: The roentgenograms and the clinical picture together suggest blastomycotic pneumonia. This disease could result in death in six to eight weeks. Usually, of course, the fungus infections are slower. Aspergillosis could also give this roentgenological picture. The aspergillosis cases that I have seen have been associated with other diseases, not necessarily lymphomas. I recall a case I saw several years ago at the St. Louis City Hospital in a young diabetic patient. In this particular community we think of blastomycosis and of histoplasmosis first. This however is an unusual picture for the acute type of histoplasmosis. Cryptococcosis, always a possibility, usually presents with some meningeal involvement. In summary, however, blastomycosis and aspergillosis would be the two diseases that I think of first.

DR. REINHARD: In September of 1955 at a clinico-pathologic conference, a patient was discussed who had terminal aspergillosis of the lung. The patient's primary disease was leuko-sarcoma. These are the roentgenograms. You will note on these films that, as in the patient

we are discussing today, there are somewhat round lesions, a fuzzy outline and a total picture not too dissimilar from the case being discussed. Dr. Beeson, are there any specific infections other than fungal infections you would like to consider? Bacterial? Viral?

DR. Beeson: Well, tuberculosis probably deserves some consideration. The appearance of the lesions does not suggest acid fast infection. The short duration of streptomycin therapy and failure to respond would not seem to me to rule it out. I cannot think of any other infections.

DR. REINHARD: Would you list tuberculosis as your first diagnosis in this case?

DR BEESON: No.

DR. REINHARD: We do not seem to be wholly satisfied with the diagnosis of neoplasm or infection. I would therefore like to concentrate your attention on the diagnosis of reticuloendotheliosis which was suggested by the pathologist on the basis of the lymph node biopsy. There is no group of disorders in the whole field of medicine in which the terminology is more confused. The term reticuloendotheliosis is used by some authors to refer to malignant neoplastic disorders of the reticuloendothelial system whereas most authors use this term to refer to various cases of Schüller-Christian disease. Letterer-Siwe disease and/or eosinophilic granuloma of bone. Considering the latter three diseases, there is considerable overlap and a multitude of other terms have been employed to describe such cases. As an example of the confusion in the literature, I would like to quote the title of an article by Pinkus\* "Reticulogranuloma: Report of a Case of Eosinophilic Granuloma of Bone Associated with Non-lipid Reticulosis of the Skin and Oral Mucosa Under the Clinical Picture of Schüller-Christian Disease." Now in order to avoid getting lost in a sea of confused terms, I would like to adhere to a classification which might be mentioned very briefly. Lichtenstein† considers eosinophilic granuloma of bone, Letterer-Siwe disease and Schüller-Christian disease all to be manifestations of the same underlying entity; this concept

is now widely accepted. He calls these all histiocytosis X. Eosinophilic granuloma of bone has been described primarily in infants, children and young adults, but occasionally it does occur in older adults as in one of our previous clinicopathologic conference reports. Letterer-Siwe disease and Schüller-Christian disease are disseminated forms of this same underlying entity; the Letterer-Siwe syndrome being an acute syndrome seen chiefly in infants and young children while the Schüller-Christian disease is a syndrome occurring in a more chronic form, in somewhat older children and young adults and occasionally in older adults. There is a marked overlap, and all may be called histiocytosis X; then one can specify histiocytosis X, localized to bone (eosinophilic granuloma of bone, solitary or multiple); or histiocytosis X, disseminated of the Letterer-Siwe type, etc. Dr. Moore, are the manifestations in this case compatible with the general diagnosis of histiocytosis X?

DR. MOORE: Although they are compatible, there are some unusual features. The lymph node changes should have been more definite. There were no lesions of bone. In addition, when pulmonary involvement occurs, it is usually a diffuse, interstitial, pulmonary infiltration often with an alveolar-capillary block and not the kind of nodular lesion that this patient had. The diagnosis seems quite unlikely, although you are certainly correct to consider it.

DR. REINHARD: How about fever of this degree in histiocytosis X?

DR. MOORE: I cannot answer that absolutely. It is my impression that it is unusual.

DR. REINHARD: I agree entirely with what Dr. Moore has said. The type of lung lesion in this case is not typical. I could find no case reported in which the roentgenographic findings resembled those in this patient. However, there are a few cases in the literature in which the infiltration of the lung is not entirely diffuse. There may be a patchy infiltrate although this does not have nodular characteristics. Furthermore, fever has been reported in some cases but I found none as high as the fever in this case. So we have the following points against the diagnosis of histiocytosis X: (1) the nature of the changes in the chest films, (2) the strikingly high fever, and (3) the very rapid course of this patient's illness. All the adult cases of histiocytosis X with pulmonary involvement that have been reported have run a longer course than this patient showed. Thus, if he turns out to

† LICHTENSTEIN, L. Histiocytosis X. Arch. Path., 56: 84,

<sup>\*</sup> PINKUS, H., COPPS, L. A., CUSTER, S. and EPSTEIN, S. Reticulogranuloma: Report of a case of eosinophilic granuloma of bone associated with non-lipid reticulosis of skin and oral mucosa under the clinical picture of Hand-Schüller-Christian Disease. Am. J. Dis. Child., 77: 503, 1949.

have had histiocytosis X there are two possible explanations for the atypical features; (1) there might be an infection superimposed on the histiocytosis, or (2) this might be a case of histiocytosis X with manifestations that have previously not been described. It is of interest that one of the patients in Dr. Magee's study had Schüller-Christian's disease and a superimposed histoplasmosis involving the lungs as well as other organs. We have already shown you the chest roentgenogram of a patient who had both leukemia and aspergillosis. I do not believe we can go any further than to say that the findings in the lymph nodes of large numbers of pale cells that appear to be histiocytes is compatible with histiocytosis X. However, the clinical picture is not such that we can make this diagnosis readily. Does anyone have other diagnostic possibilities to suggest?

DR. GERALD DIETTERT: This patient had a long alcoholic history, laboratory signs of hepatic damage and a large liver with ascites. Hepatoma, in a cirrhotic liver with lung metastases should be considered.

DR. HARRINGTON: I would like a little discussion about why this could not be staphylococcal pneumonia. There may also have been something going on intra-abdominally. The low serum calcium suggests that the patient might have had a terminal pancreatitis. On the other hand, recent reports in the surgical literature have indicated that a low serum calcium may be found in other acute abdominal problems such as perforated ulcer or the like.

DR. REINHARD: Those are good suggestions. The patient might have had pancreatic disease. Dr. Moore, do you have any comments on the low chloride in the spinal fluid.

DR. Moore: Low spinal fluid chloride is associated with many things: brain tumor, meningismus, encephalitis, infection of the meninges of various kinds. Since the spinal fluid did not show any increase in cells, since torula organisms were not present, and since other bacterial organisms were apparently not identified, I do not see how one can go any further. Tuberculous meningitis without pleocytosis would be rare indeed.

DR. REINHARD: I would like to ask the people who have participated in the discussion to give us their final diagnosis. We will not have time to make a complete list. Dr. Beeson, what would you list as your first and most likely diagnosis in this case?

DR. BEESON: I believe the patient had primary carcinoma in the abdomen with metastasis to the lungs and superimposed infection terminally.

DR. MOORE: I think that is a very good possibility. I do not see how one can eliminate the possibility of a mycotic infection such as torula, histoplasmosis or blastomycosis. However, our laboratory has such a good record in being able to isolate the organisms when present that I find it hard to overcome that obstacle.

Dr. Reinhard: They cannot isolate a fungus when you do not give them anything to isolate it from; no adequate sputum specimen was obtained.

Dr. Moore: Agreed, but the bone marrow and ascitic fluid were cultured.

Dr. Goldman: I would place fungal infection first.

DR. REINHARD: Well, I will have to list my own diagnosis as histiocytosis X plus a mycotic infection.

### PATHOLOGIC DISCUSSION

DR. JAMES PITCOCK: The patient was a large slightly obese white man with brownish pigmentation of the exposed areas of skin. There were 150 ml. of fluid in the peritoneal cavity, 750 ml. of clear yellow fluid in the right pleural cavity and 500 ml. of the same in the left pleural cavity. The heart was slightly enlarged, particularly the left ventricle, weighing 450 gm. An interesting accessory finding was the presence of a brachiocephalic artery which arose from the right innominate artery and left common carotid. The lungs were heavy, weighing 2,350 gm. Throughout all lobes were indistinct demarcated nodules about 0.5 cm. to 2 cm. in size. Some abutted on the pleural surface. On cut surface they were gray, granular and firm. Some had yellowish white centers, a little softer than the surrounding tissue. The parenchyma around these soft areas was slightly reddened. Intervening parenchyma was darker from which fluid could be easily expressed. Lymph nodes of the lungs were enlarged, homogeneous and black from anthracotic pigment.

The kidneys were congested. The firm, yellow liver was greatly enlarged (2,750 gm.). It cut with increased resistance. Its architectural pattern was prominent and delineated by increased amounts of fibrous tissue around lobules. Hemorrhage marked the site of needle biopsy.

The spleen was greatly enlarged weighing

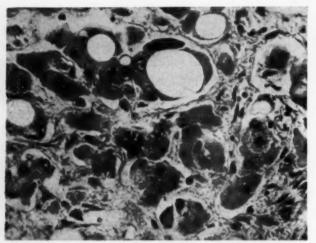


Fig. 2. Liver, hematoxylin and eosin stain. Large fatty cysts are regressing as shown by their thickened multinuclear walls. Fibrosis and regeneration are advanced.

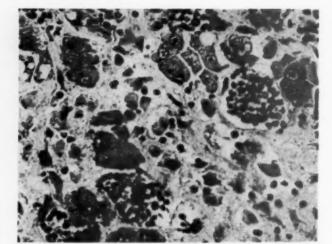


Fig. 3. Liver, hematoxylin and eosin stain, showing tract of needle biopsy two weeks before death. Vascular granulation tissue and regenerating liver cells are present.

850 gm. It was soft, mushy and dark red. There was 0.5 cm. poorly circumscribed granular nodule which was lighter in color than the surrounding tissue. Focal fat necrosis surrounded the pancreas. The bladder contained cloudy urine and its wall was heavily trabeculated. The urethra and trigone were covered by a shaggy yellow membrane. Purulent fluid oozed from the cut surface of the prostate. In the esophagus were several linear erosions and in the stomach, two shallow ulcers (2 and 4 cm. in diameter), which appeared acute in nature and recent in origin.

DR. W. STANLEY HARTROFT: The autopsy like the clinical history focused around the gastrointestinal tract, to a lesser extent the urogenital and finally the respiratory and hematopoietic systems. I will deal with them in this order. According to the history, this man indulged in excessive alcohol intake for twentyfive years. This pastime was reflected in his liver because there was a very severe degree of cirrhosis characterized by fibrosis, by abnormal accumulation of fat and by a rather striking degree of regeneration. (Fig. 2.) Fibrous tissue and abnormal accumulation of fat were present in non-portal regions according to our definition of the liver lobule and the regeneration was present in periportal. The patient had had a hepatic biopsy approximately sixteen days before death; Figure 3 shows the tract of the needle. It is surprising that after two weeks, hemorrhage still looked relatively fresh although granulation tissue had formed and perhaps more importantly, very definite evidence could be seen of

regeneration of liver cells. The rapid regeneration of the parenchyma should be of considerable comfort to those engaged in performing liver biopsies.

The lesions in the pancreas in alcoholism are just as constant and consistent, I think, as those in the liver, as is well illustrated in today's case. Throughout the entire pancreas (Fig. 4) the acinar tissue had regressed and atrophied with widening of the interacinar spaces, and increase in stroma throughout, presenting a classic picture of chronic pancreatitis including evidence of some fat necrosis. The acinar cells did not look as if they could have had much function. In addition, an acute and terminal change was present in this pancreas consisting of cystic dilation of acini here and there, a change which we associate with dehydration which this patient certainly suffered during the terminal course of his illness.

The rest of the intestinal tract was of interest chiefly in the upper portion because of the esophageal erosions. At the edges of these areas, characteristic inclusions were found in the epithelium which were pathognomonic of Herpes simplex. In the stomach there were two ulcers which microscopically appeared to be actively progressing and were both acute and subacute in nature as considerable amounts of granulation tissue had formed in their bases. These ulcers were compatible with the history of one year of gastrointestinal bleeding.

From the prostate, purulent material oozed from the cut surface at the time of autopsy and microscopic section revealed an abscess in

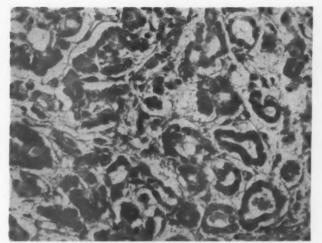


Fig. 4. Pancreas, hematoxylin and eosin stain. Atrophic and distended acini are separated by a loose stroma.

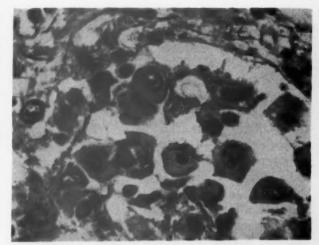


Fig. 5. Lung, hematoxylin and eosin stain. Histiocytes and mononuclear cells are present in alveolar walls (top) and lumen (center).

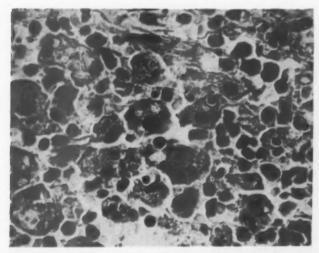


Fig. 6A. Spleen, hematoxylin and eosin stain. Foamy histiocytes fill the pulp. Erythrophogia of histiocytes is shown.

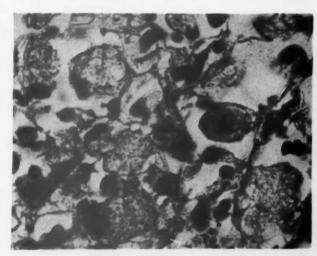


Fig. 6B. Lymph nodes, hematoxylin and eosin stain. The reticular framework is separated and the lymphoid elements replaced by large, foamy or fibrillar histiocytes.

which branching mycelia were present with subterminal spores. They proved to be Candida albicans on culture.

The lung is probably of greatest interest in this case. Microscopically, the focal areas seen grossly presented variable appearances. The alveoli were filled with masses of fibrin and red blood cells. The alveolar septums were prominent and abnormally cellular. (Fig. 5.) The cells were histiocytes probably derived from alveolar septal cells as described by Professor C. C. Macklin a good many years ago. They are part of the reticuloendothelial system therefore. Special stains revealed that the fibrin component of these lesions was considerable. In some regions hemorrhage and necrosis had developed terminally in these foci. The histiocytes frequently exhibited

beautiful examples of erythrophagia indicating their macrophagic nature. Similar foci to those in the lungs were present in spleen and lymph nodes. (Fig. 6.) Here, there were also good examples of erythrophagia. We had sections of many lymph nodes. The architecture of these was masked but not destroyed with a diminution of lymphoid elements possibly due to the chemotherapy the patient received. In addition, focal collections of foamy histiocytes were present some of which contained neutral fat in suitable preparations.

Correlation of some of signs and symptoms with the autopsy findings is of interest. Twenty-five years of alcoholism certainly had an effect on his liver and his pancreas and possibly was a factor in producing gastric ulcerations as well.

Fever and cough of some three months' duration were accounted for anatomically by the extensive involvement of the lung by the histiocytic proliferation of unknown etiology. We cut many sections and were able to rule out completely any fungi that are usually identifiable such as histoplasmosis, etc. Our cultures were essentially negative. We had no reason therefore to suspect glanders or melioidosis. The extensive nitrogen mustard and antibiotic therapy may have been responsible for the terminal ulcers of the esophagus, the prostatic abscess, the cystitis, necrosis of lymph nodes and possibly the foci of necrosis in the lungs and depression of bone marrow which I did not demonstrate. We believe this man suffered from an atypical case of histiocytosis and alcoholism with cirrhosis and pancreatitis. We believe that chemotherapy and antibiotics considerably altered the histologic and cytologic character of the histiocytosis. The alcoholism perhaps explained the unusually rapid course of the disease in an adult and the fact that the disease had not yet affected other organs than lungs, lymph nodes and spleen. We have no reason to think that this histiocytic response was associated with any specific infection. It probably belongs to that group known as histiocytosis X or Klemperer's\* reticuloendotheliosis.

Final Anatomical Diagnoses. Primary: Histiocytosis limited to lungs, spleen and lymph nodes [inguinal and femoral (biopsy), tracheal and peripancreatic]; lymphoid depletion of tracheo-

\* Klemperer, P. Reticuloendotheliosis. Bull. N. Y. Acad. Med., 30: 526-537, 1954.

bronchial and peripancreatic lymph nodes with focal necrosis (also present in pulmonic lesions) and suppression of myelocytic elements in bone marrow (history of nine days of nitrogenmustard therapy); fatty cirrhosis and chronic alcoholism, twenty-five years; atrophy and dilatation of pancreatic acini; congestion and edema of the lungs, marked: mucus in the bronchial tree; acute tracheobronchitis; patchy atelectasis, all lobes; acute gastric ulcers (2 cm. and 4 mm.) (history of melena, one year); altered blood in the large bowel, small amount; edema of the extremities and scrotum; congestion of the kidney; acute membranous cystitis; C. albicans cultured; acute prostatitis with C. albicans by culture in the tissues; petechiae of the stomach, bladder and renal pelves; unhealed left abdominal paracentesis incision; esophageal ulcerations and erosions with intranuclear inclusions bodies compatible with Herpes simplex in the margins. Accessory: arteriosclerosis of the aorta and of the coronary, splenic and cerebral arteries, slight; sclerosis of the anterior leaflet of the mitral valve, slight; focal fibrosis of the mitral and tricuspid valves; arteriolar nephrosclerosis, slight; hypertrophy of the heart; 450 gm.; brachiocephalic artery; pulmonary emphysema, slight; healed needle mark of the right upper quadrant of the abdomen; focal hemorrhage in the liver (history of needle biopsy of the liver, surgical path. No. 57-1379); nodular hyperplasia of the prostate, slight; trabeculation of the bladder; intradermal nevus of the left flank; striae abdomenoles; vesicles of the left flank (related to adhesive tape).

# Generalized Scleroderma Associated with Chronic Ulcerative Colitis\*

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Scleroderma is a "collagen" disease of unknown etiology, characterized by atrophy of the skin, vasospastic phenomena, arthritis and visceral involvement of the esophagus, lungs, heart and kidneys in more than 50 per cent of cases [1]. This report is presented to illustrate (1) generalized scleroderma associated with symptoms and signs of ulcerative colitis; (2) the spectrum of collagen diseases presented by this patient; (3) the failure of steroid hormones to improve the course of the disease; and (4) certain complications of steroid therapy.

#### CASE REPORT

V. S. (AMBH No. 52 41 39), a twenty-four year old white, single, female art student, was first admitted to Billings Hospital in April, 1950, with the chief complaints of diarrhea, joint and muscle pain and skin rashes of three years' duration. She had been well until 1945 when, at the age of fourteen, weakness, weight loss and bilateral exophthalmos developed. Radiation to the thyroid caused disappearance of all symptoms; the exophthalmos was unaffected. Three years later, dull aching pain developed in the shoulders, back and arms, which was followed shortly thereafter by severe cramping abdominal pain and bloody diarrhea. The diagnosis of ulcerative colitis with anemia was made in July, 1948, and confirmed by x-ray and proctoscopy. Treatment included iron, folic acid, sulfonamide drugs and a bland diet. By December, 1948, the patient was passing eighteen bloody bowel movements daily. The diarrhea gradually subsided, only to recur in April, 1949. She continued to have five to six bowel movements per day until April, 1950, when first admitted to Albert Merritt Billings Hospital.

Three months after the initial onset of diarrhea the patient noted increasingly severe fatigue and general malaise. Exposure to cold caused blanching, numbness and pain in the fingers. Generalized muscle stiffness and pain appeared and became progressively

worse. Intermittent bouts of cervical lymphadenopathy, sore throat and dysphagia occurred in the spring of 1950. Transient skin rashes appeared on the legs. Eighty units of ACTH given daily for three weeks in June, 1950, relieved the symptoms; however, cessation of therapy was followed by severe exacerbation.

Three months later an egg-sized, painful and tender mass appeared in the left popliteal fossa. Small, painful nodules developed over the elbows and metacarpal phalangeal joints. Three months later the patient began to experience migrating arthralgia, with occasional red, hot and tender swellings of the ankles, elbows and fingers; joint movements became restricted. In addition, she described episodes of chills and low grade fever, followed by temporary relief of the joint and muscle pain. For six months prior to admission she had been bedfast and had lost 20 pounds in weight.

Physical examination revealed an emaciated, chronically ill woman. The blood pressure was 100/65 mm. Hg; the pulse rate was 82 and the temperature was 37°c. The skin was dry, smooth and pale, with some thickening and loss of wrinkling over the forehead. An acneiform rash was present on the face. There was bilateral exophthalmos. The epitrochlear lymph nodes were palpable and tender. There was decreased fremitus and dullness in the right posterior lung base. The heart was not enlarged; the pulmonic second sound was louder than the aortic sound; soft systolic apical and basal murmurs were easily audible. Abdominal examination was not remarkable. Movement of practically all the joints was painful; lateral jaw motion was restricted. The knees were hot. The fingers were hyperextensible and slightly clubbed. Tender, red nodules, 3 to 5 mm. in diameter, were present over the metacarpophalangeal joints.

Laboratory data included a negative serum Kahn test. The white blood cell count was 7,800 per cu. mm.; hemoglobin 10 gm. per cent; red blood cell count 3.7 million per cu. mm.; hematocrit 34 per cent; sedimentation rate 38 mm./hour; and the differential was normal. Urinalysis revealed 1 plus albuminuria, which subsequently cleared. The non-protein nitro-

<sup>\*</sup> From the Department of Medicine, University of Chicago, Chicago, Illinois.

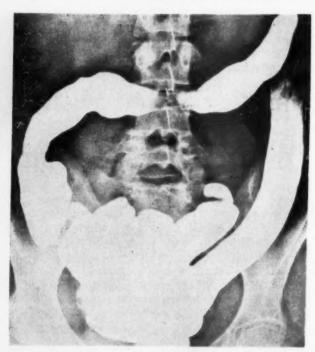


Fig. 1. Barium enema examination showing involvement of the entire colon with lack of haustrations, shortening and some marginal serration.

gen was 16 mg. per cent; the serum electrolytes, calcium and phosphorus were normal. The total plasma proteins were 8.5 gm. per cent; albumin 4.4 gm. per cent; globulin 4.1 gm. per cent. Cephalin and thymol flocculation tests were negative. The feces gave 4 plus reactions for occult blood. There were non-specific changes in the electrocardiogram. The basal metabolic rate was minus 2 per cent. Examination of the bone marrow revealed increased plasma cells and lymphocytes; no L. E. cells were demonstrable. Proctoscopy revealed a granular, moderately friable, bleeding mucosa. X-ray examination disclosed a normal esophagus, stomach and duodenal bulb. The colon manifested loss of haustration, rigidity, mucosal ulceration and marginal serration, consistent with ulcerative colitis involving the entire bowel. (Fig. 1.) Initial x-rays of the chest demonstrated slightly accentuated bronchovascular markings bilaterally, especially on the right; subsequent films revealed increasing pulmonary infiltrates, compatible with fibrosis or congestion. Skin and muscle biopsies were not diagnostic. Biopsy of a nodule on the elbow was consistent with the diagnosis of rheumatoid arthritis. Cultures of the blood, urine, nose and throat and feces were negative for pathogenic bacteria. A diagnosis of scleroderma was considered but not established definitely at this time.

The clinical course was characterized by frequent bouts of chills, fever to 40°c., an intermittent maculo-papular rash on the extremities, frequent bloody bowel movements and generalized arthralgia and myalgia. The patient's response to ACTH in amounts up to 200 units per day was poor. Definite sensitivity

to the drug was demonstrated by positive skin tests; this sensitivity included hog, beef and sheep ACTH from several companies. Administration of corticotropin produced generalized urticaria, chills, fever and increased joint pain. The clinical response to cortisone was only fair. Clinical signs of pleural effusion, myocarditis and pericardial effusion appeared. Microscopic hematuria was noted on several occasions. After nine months of hospitalization the patient was discharged as moderately improved on a regimen comprising a bland diet, sulfonamides, phenobarbital and belladonna, codeine, large amounts of salicylates and cortisone.

She was observed in the outpatient department for fifteen months and maintained on cortisone in doses of 150 to 300 mg. daily. There were frequent bouts of fever, joint swellings and diarrhea during this period but arthralgia and myalgia were the major symptoms. From this time on, symptoms of colitis were of relatively minor importance, but always present. A trial of phenylbutazone was unsuccessful, for the drug produced skin rash and fever. She also had sensitivity to various sulfonamides.

The patient was rehospitalized in February, 1953, complaining of joint pains and swelling, anorexia, exertional dyspnea, painful blanching of the fingers on exposure to cold, and diarrhea. Physical examination revealed a "moon-faced," emaciated, chronically ill woman, who sat with her head and neck held stiffly; movement of any kind was slow and painful. The anterior and posterior cervical lymph nodes were enlarged. Rales were audible over both lung bases. Painful nodules were present on both wrists; the knees and ankles were swollen. The white blood cell count was 8,500 per cu. mm.; hemoglobin was 11.6 gm. per cent; the differential blood smear was normal; sedimentation rate 47 mm./hour. The basal metabolic rate was plus 1 per cent. The urine was normal. The values for serum albumin and globulin were 3.0 and 4.6 gm. per cent. Benzidine tests of the feces gave 0 to 4 plus reactions. Several examinations for L. E. cells in the peripheral blood were negative. X-rays of the chest revealed pulmonary fibrosis. X-rays demonstrated osteoporosis of the knee joints and reduced excursion of the left temperomandibular joint. The course was characterized by frequent bouts of fever, joint pain and stiffness. The patient experienced periods of marked depression and psychotic episodes, always responding to reduction in the dosage of steroids. Several attempts to withdraw cortisone caused increased fever, joint pain and swelling. After five months of hospitalization she was discharged on 150 mg. of cortisone per day. During the next five months loss of sensation, paresthesia, swelling and pain in the fingers developed. Breathing became increasingly difficult. The quantity of cortisone was increased gradually to 400 mg. per day; salicylates were administered to the point of toxicity.

In November, 1953, she was readmitted in moribund condition, two days after the onset of bright red

hematemesis and melena. The blood pressure and pulse were unobtainable. Emergency operation revealed a briskly bleeding duodenal ulcer, penetrating into the pancreas; a subtotal gastrectomy with anterior gastroenterostomy was performed. There were no changes of scleroderma in the resected specimen. The gastric mucosa contained scars of healed ulcers and a shallow active ulceration. She was discharged one month later on a regimen of 50 mg. cortisone per day.

The patient then was observed for five months in the outpatient department. Joint pains continued to predominate the clinical picture. Hydrocortisone was given in doses up to 150 mg. per day with little beneficial effect. Epigastric pain developed and continued day and night. Four months after this hospitalization, a persistent respiratory infection developed and she began to cough large amounts of whitish mucoid material. Two weeks later, fluoroscopy revealed a pleural effusion. Orthopnea became very pronounced and she was readmitted to the hospital in May, 1954. Physical examination revealed dullness over both lung bases, increased fremitus at both bases, diminished diaphragmatic excursions, coarse rales in the left apex and distant breath sounds. An erythematous rash was present on the trunk and arms. X-ray examination of the chest revealed diffuse parahilar infiltration and scarring. There was osteoporosis of the thoracic spine with a compression fracture of T-12. The feces gave 1 to 2 plus reactions for occult blood. Cultures of the sputum were negative for pathogens. Diuretics, digitalis and antibiotics were ineffective. The patient was discharged two months later on a dose of 100 mg. hydrocortisone per day.

She was readmitted in August, 1954, complaining of vomiting, hoarseness, cough, dyspnea, weight loss and joint swellings. An erythematous maculopapular rash was present over the back and chest. Mandibular motion was restricted. Respiratory movements were rapid, irregular and shallow. Rales and coarse rhonchi were audible throughout the chest. Aortic systolic, left parasternal systolic and apical systolic murmurs were present. Two weeks later, friction rubs were heard over the left anterior and right anterior lung bases. The white blood count was 14,000 per cu. mm.; and hemoglobin 9.9 gm. per cent; and sedimentation rate 56 mm./hour. The urine contained a trace of albumin and red blood cells. The protein bound iodine was 2.6 µg and the basal metabolic rate plus 7 per cent. The patient was given 30 mc. of I131 in an effort to retard the progress of the scleroderma. She was discharged one month later. In December, 1954, she suffered a fracture of the neck of the left humerus, secondary to osteoporosis and trauma.

The final admission on February 20, 1955, was because of severe weakness, productive cough, dyspnea and diarrhea. The blood pressure was 90/50 Hg and the pulse rate was 132. There was severe orthopnea with marked respiratory distress; the temperature was elevated. Other symptoms were constant

drooling of thick, tenacious mucoid sputum and frequent cough. Coarse rhonchi and fine rales were audible at both bases. There was dullness and decreased fremitus at both bases. The hemoglobin was 7.3 gm. per cent and white blood count 4,900 per cu. mm. The urine contained 1 plus albumin, occasional red blood cells and many leukocytes. The feces were positive for occult blood. Treatment included oxygen, blood transfusions, tracheal aspiration and cortisone. The patient remained lethargic and grew steadily worse. Death occurred five days after admission because of respiratory failure.

At autopsy (performed by Dr. B. Spargo three and a half hours after her death) the patient was markedly emaciated. The gross findings included bilateral exopthalmos with scleral ulceration, shiny atrophic skin over the chest and forearms, a recent tracheotomy incision, generalized edema of the trunk with serous atrophy of fat, fusiform swellings of the left elbow and left knee and arthritic changes in the metacarpal-phalangeal joints of both hands. There were decubitus ulcers on the sacrum and right hip and a well healed epigastric scar.

The thyroid was small, fibrotic and stony hard. The lungs were congested, firm, dark red and gritty on cutting. There were dense pleural adhesions, with loculated pleural effusions which contained up to 150 cc. of serous fluid. Examination of the heart revealed thickening of the chordae tendinae of the mitral valve. The esophagus was thickened uniformly. Superficial mucosal ulcers were present in the distal one-third of the esophagus. The stomach contained a well functioning gastroenterostomy and thickened walls. The colon had an increasingly narrowed lumen with a circumference of 4 cm. at the cecum and 3 cm. at the sigmoid. The bowel wall was progressively thickened from the cecum to the sigmoid. In the distal 18 inches of ileum, the mucosa was hyperplastic and contained small superficial ulcerations. No gross ulcerations were present in the colon. The adrenals were thin and atrophic.

Microscopic examination revealed scleroderma of the skin (Fig. 2) with flattening of the epidermis and deposition of dense acellular collagen in the dermis. There was diffuse fibrosis in the lungs, with distention of alveoli by mucus. The bronchioles showed focal proliferation, and sclerosis of small-sized pulmonary vessels was apparent. There was extreme atrophy of the adrenal cortex, especially in the zona fasciculata, and hyalinization of arterioles. Hydropic and colloid changes were noted in the proximal convoluted tubules of the kidneys. Proliferative and degenerative changes were observed in the arterioles. No follicles were seen in the thyroid, which was replaced by dense fibrous tissue. The pituitary contained an increased number of eosinophils and enlarged basophils, with loss of pigment and central vacuolization (Crooke's changes). Passive congestion was present in the liver and spleen. Areas of focal fibrosis and infiltration by plasma cells and lymphocytes were

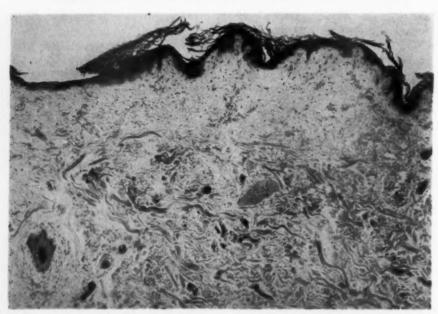


Fig. 2. Section of the skin. Atrophy of the epidermis. The thickened dermis shows deposits of hyaline, curled collagen masses. Original magnification,  $\times$  100.

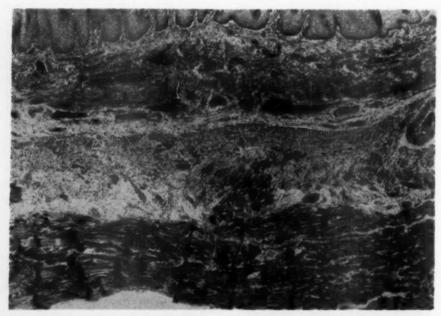


Fig. 3. Lower part of the esophagus. There is diffuse cellular infiltration in the submucosa, vascular engorgement and fibrous replacement of the inner layer of the muscularis propria. Original magnification,  $\times$  52.

present in the heart. Changes suggestive of early demyelinization were noted in peripheral nerves, but the brain showed no focal changes. In the lower esophagus there was thickening of the mucosa, hypertrophy of the muscularis mucosae and pronounced inflammatory infiltration of the lamina propria and submucosa. (Fig. 3.) The internal muscle layer was largely replaced by fibrous tissue. There was venous stasis and thickening of arteriolar walls. Cellular infiltration was present in the lamina propria of the small bowel. The muscle layers stained with

differing intensity. The colon also manifested increased cellularity in the lamina propria. There were microscopic areas of superficial ulceration; other sites had a cuboid type of surface epithelium which was indicative of regeneration. The muscularis mucosae was hypertrophic and the submucosa was widened and infiltrated with fat. The muscularis propria was hypertrophic. In one microscopic area there was an infarct-like appearance, with muscle atrophy and replacement by connective tissue. (Fig. 4.) Acellular collagen was noted in small areas in the

submucosa. The intima of the blood vessels was thickened and the media fibrotic. The serosa was thickened diffusely.

#### COMMENTS

Gastrointestinal involvement in scleroderma is well documented [1,2,3]. Hypomotility, esophageal dilatation, constriction, atrophy of muscles and collagenous replacement of submucosal tissues cause dysphagia, the principle and often the only symptom of gastrointestinal scleroderma [4]. Histological evidence of esophageal scleroderma frequently is present despite the absence of clinical manifestations [5].

Careful roentgenological and microscopic studies of small groups of patients with scleroderma have demonstrated involvement of both the small and large intestine [6,7,8]. Roentgen observations in the small intestine have included local areas of widening, puddling, dilated loops and delayed passage of barium. In most cases, these findings have been associated clinically with nausea, vomiting and constipation and partial intestinal obstruction. Sclerodermatous involvement of the colon has rarely been reported and almost never associated with clinical findings [9]. Hale and Schatzki [10] described two patients with sacculation and localized rigidity of the colon, as seen by x-ray. In one patient this was accompanied by crampy abdominal pain and diarrhea; sigmoidoscopy revealed no abnormalities. In the report of a fatal case [11], the colon demonstrated mucosal atrophy and collagenous replacement of the smooth muscle of the descending and sigmoid colon. Proctoscopy had been negative but the patient died of gangrene of the bowel secondary to thrombosis of major arteries.

In an autopsy series of thirty-one cases [1], fibrotic, rigid segments of the colon, associated with mucosal inflammation and ulceration, were noted in two patients. Sixty-four per cent of the patients in this series had gastrointestinal involvement, mainly esophageal. Other lesions included mucosal ulceration with inflammatory infiltrates and sclerosis of the submucosa of the stomach, and fibrosis and sclerosis of the submucosa of the small bowel. Of six colons examined, two were normal, two had fibrosis of the submucosa and two had findings similar to those noted in the present case.

Kemp-Harper [13] found definite roentgenological abnormalities in the colon in eight of eleven patients. These consisted of an asym-



Fig. 4. Colon. Fibrous replacement of the external layer of the muscularis propria. Original magnification, X 65.

metrical outline of the bowel, with haustration on one side and wide-mouthed diverticula on the other; these pouches remained open and filled with barium after evacuation. Changes were found in patients with or without gastro-intestinal symptoms. In one patient examined at necropsy, the severe involvement of the descending colon resembled ulcerative colitis. Clinically, there were no symptoms of ulcerative colitis, and sigmoidoscopy had demonstrated a gray, "sclerodermatous" mucosa in six of the eleven cases. Cullinan [14] believes that this is a characteristic finding of scleroderma at proctoscopy.

In the present case, signs and symptoms compatible with ulcerative colitis apparently preceded the dermal manifestation of scleroderma by at least five years. Careful, repeated roentgen and proctoscopic studies of the colon by experienced observers were interpreted as characteristic of ulcerative colitis. The important anatomic features of ulcerative colitis are mucosal ulceration with islands of glandular hyperplasia and infiltration with acute and

chronic inflammatory cells [12]. The present patient manifested many of these features which were consistent with the microscopic diagnosis of ulcerative colitis: infiltration of the lamina propria, ulceration, thickening of the submucosa with deposition of fat, general thickening of the intestinal wall and narrowing of the lumen. The patchy deposition of collagen in the submucosa and arteriolar fibrosis, fibrous replacement of the external muscularis and thickening of the serosa are suggestive of scleroderma. Features of both diseases were apparent in the present case. This is consistent with the observation that the basic pathological process of collagenosis may involve any organ with connective tissue, the signs and symptoms depending on the organ involved [15].

The entire gamut of collagen diseases emerged during this patient's course. The clinical diagnoses of rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis and scleroderma were suggested at various times. At least two of these diseases, rheumatoid arthritis and scleroderma, were proved histologically. The multiple organs that were affected, i.e., muscle, bone and joint, skin, heart, kidneys, pleura and colon, are characteristic of diffuse collagen disease [16]. Eight L. E. preparations were negative; two skin biopsies were normal. Biopsy of a skin nodule during the phase of active ulcerative colitis was consistent with the diagnosis of active rheumatoid arthritis. This overlapping of clinical syndromes of collagen disease has been reported previously [17].

A possible relationship of ulcerative colitis to diffuse collagen diseases, because of anatomical changes in the basement membranes of the connective tissue of the rectum as noted in biopsies of patients with ulcerative colitis, has been suggested previously [18]. A common feature of patients with ulcerative colitis and diffuse collagen disease is the frequency and severity of allergic reactions to blood transfusions and various drugs. Both of these diseases may be related to the hypersensitivity state although there is no conclusive evidence at present [20,21].

Apart from the lack of effect upon the relentless course of the scleroderma, serious complications were produced by corticotropin, cortisone and hydrocortisone. There were the usual physical and electrolyte changes associated with steroid-induced Cushing's syndrome: "moon facies," acne, edema, hypokalemia, hypernatremia and hypochloremic alkalosis [18]. Adrenal cortical atrophy and Crooke's changes in the pituitary basophils were observed histologically. Steroid-induced psychosis, noted in approximately 5 per cent of patients with ulcerative colitis given steroids [22], also developed in this patient. The psychosis was manifested by agitation, depression and extreme emotional lability. It always subsided after rapid reduction in dosage of the steroids; however, this decrease invariably was followed by an exacerbation of the symptoms of fever, arthralgia and diarrhea.

The massively bleeding duodenal ulcer which necessitated emergency surgery was another dramatic complication. The ulcer was a penetrating lesion associated with poor inflammatory response; scars of healed shallow gastric ulcers were also noted histologically. True peptic ulceration has been estimated to occur during the lifetime of 10 per cent of the population [23]. It has been described also as a complication of steroid therapy [24]. However, there is no conclusive evidence as yet that the frequency of "steroid-ulcer" significantly exceeds the expected incidence of peptic ulcer in chronically ill patients. In this patient no significant changes were noted in gastric secretion before subtotal gastric resection. It should be noted that there was no recurrence of ulcer or symptoms despite an inadequate gastric resection and despite the continued administration of large amounts of steroids. It is of interest that in a young woman of similar age with severe ulcerative colitis. shortly after the present patient was operated upon, a large duodenal ulcer with intractable hemorrhage developed, which also required surgical management. However, in contrast to the present case, the second patient had never received steroids.

Bone surveys demonstrated generalized osteoporosis. The last year of the patient's life was complicated by compression fractures of the thoracic vertebrae and of the left humerus. The mechanism of this relatively rare [25] complication of steroid therapy is not clear, but seems to be related to the antianabolic effects of the adrenal steroids. It occurs most commonly in postmenopausal women on limited activity and prolonged therapy. Generalized osteoporosis is a prominent finding in Cushing's disease [26].

Corticotropin and cortisone have been administered successfully in the treatment of both ulcerative colitis and scleroderma [27,28]. Perhaps "non-specific" ulcerative colitis encom-

passes diseases of varying etiology, including undetected viral infections, collagen disorders and still other undefined types [29]. The differing pathogenic mechanisms may explain, in part at least, the failure of otherwise potent steroid therapy to influence the course of ulcerative colitis in all patients. The present case suggests the desirability of careful investigation of each patient with apparently non-specific ulcerative colitis for possible specific etiologic factors.

### SUMMARY

A case of generalized scleroderma associated with the clinical syndrome of non-specific ulcerative colitis is presented. The diagnosis was difficult to establish clinically and pathologically. The clinical course was characterized by a spectrum of collagen diseases that included systemic lupus erythematosus, rheumatic fever, rheumatoid arthritis, dermatomyositis and scleroderma. The patient received 11,000 units of ACTH, 48,000 mg, of hydrocortisone and 162,000 mg. of cortisone over a period of five years without significantly influencing the relentless course of the disease. The following complications of steroid medication developed: Cushing's syndrome and adrenal cortical atrophy, steroid psychosis, peptic ulcer and osteoporotic fractures of the vertebrae and humerus.

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# Bilateral Adrenal Hemorrhage Complicating Dicoumarol Therapy for Myocardial Infarction\*

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**B**ILATERAL adrenal hemorrhage complicating anticoagulant therapy is rare. I have found only two autopsied cases in the literature and one presumptive case [17,33]. In all of these heparin was the anticoagulant used.

The following case is one in which bilateral adrenal hemorrhage occurred during dicoumarol therapy for myocardial infarction.

#### CASE REPORT

Patient H. M., a fifty-five year old white man, was admitted to The Mountainside Hospital on October 10, 1956 with a history of "blackout" while returning home from work. The week prior to admission he noted fatigue, with a sense of uneasiness in the anterior chest, but no pain. His skin was moist and cool, his nail beds were cyanotic. The blood pressure immediately after the "blackout" was 90/60 mm. Hg but it soon rose to 120/70 mm. Hg. The pulse was 100 per minute and irregular. The head and neck were within normal limits. The heart sounds were distant, no thrills or murmurs were present. Moist medium rales were heard at the lung bases. There were no abdominal masses and the liver, kidney and spleen were not palpable. An electrocardiogram was taken and interpreted as consistent with a posterior wall infarction, with flutter-fibrillation. The patient was digitalized with digoxin, and heparin and dicoumarol were given. The heparin was stopped when the dicoumarol took effect. Other therapy included a low salt diet, demerol for extreme restlessness or pain, nasal oxygen, sedatives, and a combiotic late in the hospital course when a pneumonitis could not be excluded. Papaverine 1 gr. administered intramuscularly every four hours, was given beginning on October 22, 1956, when embolization to the left leg was considered. At 12 noon on October 20, 1956 equanil® was given for the extreme apprehension the patient exhibited. It was stopped at 8 P.M. on October 21; thorazines, \$\text{\$\text{\$\text{\$\text{\$}}}\$ 25 mg. intramuscularly, was given on October 22, for two doses six hours apart.

Laboratory findings on admission were as follows: hemoglobin, 13.6 gm. per cent; red blood cells, 4.0 million per cu. mm.; white blood cells, 10,500 per cu. mm. with polymorphonuclear leukocytes, (PMN) 76 per cent; lymphocytes, 18 per cent; monocytes, 3 per cent; eosinophils, 0; basophils, 0.

Daily white blood counts and differential counts indicated a mild leukocytosis, with an average count of 12,500 per cu. mm. and PMN predominance (average, 84 per cent) which subsided to normal until the last four days of life. On October 19, 4 per cent eosinophils were noted with a white blood count of 9,000 per cu. mm. On October 20 the white blood count soared to 18,300 per cu. mm. with 94 per cent PMN, 5 per cent lymphocytes and 1 per cent monocytes. On October 21 the white blood count was 11,330 per cu. mm. with 78 per cent PMN, 20 per cent lymphocytes and 2 per cent eosinophils. On October 22, the white blood count rose to 21,600 per cu. mm. with 89 per cent PMN, 10 per cent lymphocytes, and 1 per cent monocytes. The erythrocyte sedimentation rate on admission was 6 mm. in the first hour, but it rose rapidly to 92 mm. and remained in that range until the last two days of life; it was 35 mm. on the last day of life (October 23). Serial electrocardiograms showed evolutionary changes with gradual slight improvement until October 22, when evidence of extension of the infarct with a marked increase in the elevation and depression of the ST segments, especially in leads III, AVF, V2, 3, 4, 5 and 6. A serum transaminase taken on the morning of October 23, the last day of life, was 26 units (normal).

The prothrombin times were as follows: October 11, 16 seconds; October 12, 19 seconds; October 13, 19 seconds; October 14, 23 seconds; October 15, 32 seconds; October 16, 32 seconds; October 17, 25 seconds; October 18, 19 seconds; October 19, 23 seconds; October 20, 27 seconds; October 21, 32 seconds; October 22, 25 seconds; and October 23, 25 seconds.

The patient's hospital course was characterized by extreme anxiety, nausea and restlessness. Intermittently he complained of aching pain in the chest.

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The blood pressure during his hospital stay ranged between 110/70 to 94/60 mm. Hg, until October 20. The temperature, after an initial elevation to 102°F. on October 12, remained about 99° to 100°F. until October 21. The pulse was 80 to 90 per minute until October 21.

Early in the hospital course he complained of no abdominal pain. On October 20 epigastric distress, abdominal distention and "gas-pains" developed, and he had frequent eructations. He passed flatus and felt relieved momentarily. The blood pressure increased to 134/100 mm. Hg while the pulse and temperature remained the same.

On October 21 the patient was disoriented but had no further abdominal pain although his abdomen was still distended and he was still eructating. The blood pressure was 122/84 mm. Hg, pulse 90 to 104, and the temperature increased to 102° to 103°F. There was no edema of the ankles or distention of the neck vein but rales were still present at the lung bases.

On October 22, the patient was talking loudly to himself and had hiccups and nausea. He was complaining of continuous numbness and intermittent pain in the left leg and foot. No peripheral pulsations were noted in either foot. The question of embolization to the left lower extremity arose. The patient was restless and a cold sweat developed. The temperature was now 104°F., the pulse 90 to 104 per minute, and the blood pressure had dropped to 90/60 mm. Hg.

On October 23 at 2 A.M. the blood pressure was suddenly unobtainable. The temperature remained at 104°F., while the pulse rate increased to 130 per minute. The patient's color was dusky, with cyanotic lips and nail beds. A levophed® infusion was started and the blood pressure rose to 92/72 mm. Hg. At 4 A.M. the blood pressure was again unobtainable. The infusion rate was increased and again the blood pressure rose. The abdomen was quite distended and the patient was irrational. He had no abdominal pain. The blood pressure began dropping, the levophed infusion was less effective in raising the blood pressure and at 12:30 P.M. the patient had a spontaneous bowel movement and died.

At autopsy (performed by Dr. Alfred Zettner fourteen hours after death), there was no evidence of purpura externally. There were hematomas about needle puncture wounds in both antecubital fossae.

The heart weighed 460 gm. and was moderately enlarged. On the posterior aspect of the left ventricle there were several small confluent subepicardial hemorrhages and some deep in the myocardium. Almost the entire posterior and lateral wall of the left ventricle was infarcted and there was an 0.4 cm. organizing thrombus firmly adherent to the endocardium of the left ventricle in the infarcted area. A firmly adherent thrombus occluded the lumen of the circumflex branch of the left coronary artery. Microscopically, the bulk of the infarct appeared to be three to six weeks old, with smaller foci of somewhat recent

origin. Where the infarct involved almost the entire thickness of the ventricular wall, there were central areas of muscle fiber necrosis without hemorrhage or neutrophilic infiltration, a not uncommon finding in large myocardial infarcts. There were large confluent recent hemorrhages in the para-aortic tissue in the region of the arch of the vessel.

The lungs were normal in size, shape and texture but contained a fairly large amount of edema fluid and blood which oozed from the cut surface. The pulmonary artery, venae cavae and the large veins were within normal limits.

Both leaves of the diaphragm were the seat of extensive recent hemorrhages, particularly beneath the pleural and peritoneal surfaces, and also into the muscle itself. Microscopic examination revealed sheets of erythrocytes that extended between the skeletal muscle fibers, and some of the latter showed evidence of early degeneration.

The spleen was of normal size and shape and displayed two infarcts each measuring 3 cm. across. The splenic artery and vein were within normal limits. The pancreas was normal.

The adrenals were markedly altered in size and shape. They were globular and measured about 6.5 by 5.5 by 5.4 over-all. On section they consisted of a thin shell of yellow-red cortical tissue surrounding what appeared to be a blood clot. No medullary tissue was identified. The hemorrhagic portions had a fairly uniform and homogeneous appearance, were dark red in color, friable and dry with no visible liquid blood. (Fig. 1.) Multiple sections (16) of both adrenals revealed bland thrombi in the main adrenal veins bilaterally, and thrombi were present in some of the small thin walled adjacent tributaries. These thrombi showed little or no evidence of organization. All about the occluded veins there were large sheets of erythrocytes in various stages of disintegration and a few leukocytes which together had replaced the adrenal tissue with the exception of a few remaining intact cortical cells located just beneath the capsule. In some areas of the hemorrhagic degenerating cortex there was focal heavy neutrophilic infiltration and here many of the neutrophils showed evidence of fragmentation and degeneration. In still other fields the hemorrhage was of very recent origin without any visible reaction to it. Here and there the hemorrhage extended through the capsule into the periadrenal fibroadipose tissue where there was often considerable reaction to it in the form of neutrophilic infiltration and early fibroblastic proliferation. (Fig. 2.) There was no evidence of arterial obstruction in the form of embolization or thrombosis, and only mild arteriolarsclerosis.

The kidneys were of the usual size and shape and both displayed areas of recent infarction. Microscopically, there were zones of typical coagulation necrosis and there was no arteriolar or glomerular disease. The renal arteries and veins were within

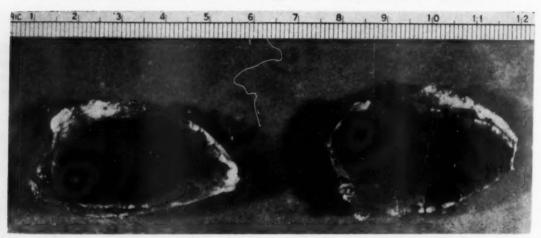


Fig. 1. Representative cross-sections of the adrenal glands. Each adrenal presents a thin rim of cortex which surrounds what appears to be a blood clot. No medullary tissue is identified.

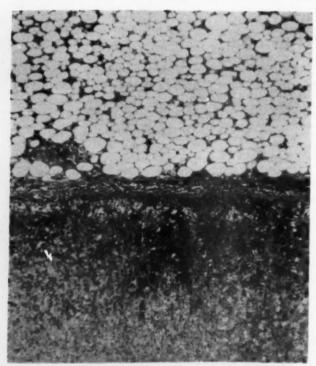


Fig. 2. Microscopic section. Periadrenal fibroadipose tissue and adrenal cortex, showing degenerating adrenal cortex with degenerating red blood cells. Original magnification,  $\times$  100.

normal limits. With the exception of microscopic recent hemorrhage into the mucosa and submucosa of the urinary bladder, the rest of the urinary tract revealed no abnormalities.

The small intestine was markedly dilated with gas. There were small scattered subserosal hemorrhages especially in the antemesenteric region of the intestinal wall.

Gross examination of the central nervous system revealed no abnormalities. A section of brain revealed hyperemia of the arachnoid and pial vessels but no other significant abnormalities. The capillaries deeper in the brain tissue likewise were filled with sheets of erythrocytes.

There was no significant lymphadenopathy. A section of vertebral bone marrow revealed no abnormalities except for a slight predominance of the granulocytic series as compared with the erythrocytic series, probably reflected in the marked leukocytosis noted on October 22. Scattered about in the marrow were numerous well-formed megakaryocytes, many of which appeared to be forming platelets.

Summary of pertinent autopsy findings: There were multiple recent hemorrhages into the para-aortic tissue (region of the arch), perirenal tissue, subserosal tissue of the small intestine and into the diaphragm. There was massive hemorrhagic infarction of the adrenal glands bilaterally with bilateral bland thrombosis of the main adrenal veins. The urinary bladder was the seat of a hemorrhagic cystitis. There was recent thrombosis of the circumflex branch of the left coronary artery with large recent infarcts of the posterior and lateral walls of the left ventricular myocardium. The organizing mural thrombus in the left ventricle may have been the source of emboli that may have caused the splenic and renal infarcts.

### COMMENTS

The blood supply of the adrenal is very profuse. Each adrenal is supplied by numerous vessels, derived from the phrenic, aortic and renal arteries, which divide as they course toward the adrenal, arborizing profusely at the margin of the gland to supply the cortical sinusoids [4]. Each adrenal is drained by only one adrenal vein [4], making it extremely vulnerable to infarction if thrombosis should occur. In adults, in the absence of septicemia, thrombophlebitis of the adrenal vein, either

primary [1] or secondary to local inflammation, or to infection, is the most common cause of adrenal hemorrhage [1,14,15,18,27].

Rich noted that various acute infections produce damage to the adrenal cortex with necrosis of isolated cells and transformation of the solid cords of the zona fasciculata into tubular structures containing an inflammatory exudate. He further noted that circulatory collapse alone did not produce these lesions [28]. Wilbur and Rich were able to produce this "tubular degeneration" in experimental animals by administering large doses of ACTH [36]. They suggest that these changes precede the hemorrhagic necrosis in overwhelming sepsis. An impression has been gained that stress itself and the adrenal stimulation which it occasions may predispose the cortex to hemorrhagic destruction. Thus one patient was reported to have died of massive adrenal hemorrhage following cholecystectomy in the absence of diffuse vascular disease, blood loss, sepsis, etc. [29].

Dicoumarol affects blood coagulation by causing hypoprothrombinemia. Bleeding is the outstanding feature of toxicity. Two components appear to be involved in the hemorrhagic syndrome: one is the hypoprothrombinemia and the other is vascular damage [12]. Bingham and his co-workers have shown in dogs that a single massive dose of dicoumarol sufficient to cause the death of the animal caused no hemorrhagic manifestations even though the prothrombin time was lowered profoundly, while repeated smaller doses did produce widespread hemorrhages, with the prothrombin time less prolonged [6].

Hemorrhage into the adrenals may result from thrombosis of the adrenal veins (and arteries), conditions affecting the coagulability of blood, and conditions causing vascular damage and/or primary damage to cortical cells. In an individual case more than one factor may be operative.

In the literature, adrenal hemorrhages have been reported in association with fatal diphtheria, burns, idiopathic thrombophlebitis of the adrenal veins [1], pancreatitis and other local inflammation [14,15,18], and with acute infections without overwhelming septicemia [14]. They have also been noted after trauma [34], surgery [29], hypertension [13,20], ulcerative colitis with [39] and without ACTH therapy [25], metastatic carcinoma [29], electroshock therapy and epilepsy [2], leukemia, overwhelming

septicemia [10,16,22,23,30,35], in the newborn and other associations [5,7–9,18,19,26,32,38].

The clinical picture of adrenal hemorrhage is variable, depending on the etiology and whether or not the hemorrhage is unilateral [11,21,24,34] or bilateral. The association of bilateral adrenal hemorrhage with overwhelming infection results in a clinical picture of headache, nausea, vomiting, diarrhea, abdominal pain, irritability, fever and at times convulsions. Shortly after the onset a generalized cyanosis appears and is followed by a purpuric rash. Evidence of a generalized hemorrhagic state is almost always present [1,10,37]. Death usually ensues within twenty-four hours unless proper therapy is given.

In contrast, the symptoms of arterial or venous thrombosis are those of an acute condition of the abdomen; purpura is usually absent. Patients are frequently operated upon in the mistaken belief that an acute abdominal episode has occurred [1,14]. Early in the hemorrhage little change in the blood pressure, temperature, pulse or respirations may be noted, in contrast to the findings in septicemia [37]. However this is not always the case. Lavenson's patient presented a picture of sudden onset of vomiting, epigastric pain, lumbar tenderness and profound shock, and died thirty-six hours after admission. There was no purpura [15].

Sudden death may be the only manifestation of bilateral adrenal hemorrhage, or the clinical picture may be dominated by delirium, convulsions and coma [15].

In the case reported by Thorn et al. the postoperative patient became lethargic and anorexic and a wound hematoma was noted during heparin therapy. The patient deteriorated and became comatose. Laboratory studies indicated a blood sugar of 43 mg. per cent; serum sodium, 123 mEq.; and an eosinophil count of 108. Replacement therapy was instituted and definitive studies afterward substantiated the diagnosis. No note is made of abdominal pain [33].

In the case summarized from the literature by Merz and Aufdermaur sudden shock and death within a few hours were the only manifestations of the hemorrhage complicating heparin therapy. In their own case the patient (seen postoperatively) was a seventy-two year old woman with cardiac failure, thrombophlebitis of the left leg, and pulmonary embolization, who was being treated with heparin. On the sixth day of heparin therapy pulmonary embolization developed at noon and in the evening sudden collapse

with vomiting occurred, followed by a crisis of hypertension and meteorism. The coagulation times were suddenly prolonged. The patient remained apathetic, vomiting persisted; the collapse could not be influenced and the patient died within three days. Autopsy revealed bilateral suprarenal hemorrhage without any evidence of thrombosis of the adrenal veins. There were scattered hemorrhages in other organs. The attack of hypertension was interpreted as probably corresponding to the onset of the hemorrhage with increased emission of noradrenalin by the cells of the medulla directly into the blood [17]. The diminished capillary resistance of old age probably plays an important part in the pathogenesis of hemorrhage [17]. The cases (3) of bilateral adrenal hemorrhage complicating anticoagulant therapy were in older individuals [17,33].

In the case presented in this paper, autopsy indicated a hemorrhagic diathesis. Hemorrhages were present in the para-aortic tissue, perirenal tissue, subserosal tissue of the small intestine and both leaves of the diaphragm. The normal bone marrow and lymphatic tissue speaks against a blood dyscrasia as the cause of

the hemorrhagic diathesis.

The adrenal glands gave evidence of severe bilateral hemorrhagic infarction. The hemorrhagic infarction was not agonal in nature in view of the reaction to the hemorrhage and the presence of degenerative changes noted in the bulk of adrenal tissue bilaterally. It is not possible definitely to exclude multiple embolization to both adrenals as the cause of the hemorrhage, considering the possibility of embolization to the kidneys and spleen. However, in view of the small size and sheltered locations of the adrenals, with an arterial blood supply that is very profuse, it is unlikely that simultaneous bilateral embolization with infarction occurred.

Thrombosis of the adrenal veins in the absence of phlebitis of the adrenal veins must be interpreted with caution. In a small number of cases of septicemia and purpura complicated by adrenal hemorrhage, adrenal vein thrombosis was found. However, in view of the rarity of this finding in these cases of adrenal hemorrhage caused by overwhelming sepsis, it is considered that thrombosis of the adrenal veins is secondary to the hemorrhage caused by severe cortical cell damage [37].

In this particular case it cannot be definitely determined whether the infarction preceded

or was caused by the adrenal vein thrombosis. It is unlikely that a bilateral localized bland adrenal vein thrombosis in the presence of a generalized hemorrhagic diathesis occurred during adequate anticoagulant therapy. Histologic examination in areas of the degenerating cortex revealed neutrophilic infiltration with many of the neutrophils showing evidence of degeneration. Where the hemorrhage extended through the capsule of the adrenal into the periadrenal fibroadipose tissue there was often considerable reaction to it in the form of neutrophilic infiltration and early fibroblastic proliferation, in contrast to the lack of reaction to the thrombi in the main adrenal veins. This suggests that the hemorrhage preceded the adrenal vein thrombosis. More likely, the adrenal hemorrhage occurred and, following this, consequent to stasis of blood, damage to the endothelium of the adrenal veins and release of tissue fluids, bland thrombosis of the adrenal veins occurred. Furthermore, the clinical picture was not that of primary adrenal artery-vein thrombosis.

In the microscopic sections the adrenal cortex showed no evidence of "tubular degenerative" changes of the zona fasciculata. There is no evidence therefore that the adrenal hemorrhages were secondary to stress although, because of the severe hemorrhagic destruction of the adrenals, these findings could have been

obscured.

In a recent article concerning anticoagulant therapy in myocardial infarction, there were forty-eight bleeding episodes requiring discontinuance of the anticoagulants. In twenty-six, or 54 per cent, of these instances the prothrombin time was above the accepted therapeutic range of the authors (two to three times the control). In 37.5 per cent of the cases the bleeding occurred when the prothrombin was adequate. However, in 8.5 per cent of the cases the bleeding occurred when the prothrombin was below the control zone [31]. It would seem therefore that the prothrombin time need not necessarily be very prolonged for bleeding to occur.

In analyzing this patient's hospital course, it is likely that the initial hemorrhage into the adrenals occurred on October 20 when the abdominal pain developed and his blood pressure increased, while his white count rose to 18,330 per cu. mm. This would correspond to the older hemorrhages noted on the microscopic sections. Then his condition stabilized temporarily, only to deteriorate rapidly when the hemor-

rhage was completed presumably on October 22 and 23.

#### SUMMARY

A case of bilateral adrenal hemorrhage complicating dicoumarol therapy for myocardial infarction is presented. At no time was the prothrombin time, which was determined every morning, above the therapeutic range. It is not possible definitely to exclude adrenal vein thrombosis as the causative factor in the hemorrhage but this is considered unlikely in view of the generalized hemorrhagic diathesis present. Other factors which may have played a role in the hemorrhage are discussed. The clinical picture, etiology and pathogenesis of adrenal hemorrhage is discussed.

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# Macroglobulinemia of Waldenström\*

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Waldenstrom in 1944 [1] described a disease entity which he later called macro-globulinemia [2]. Its characteristic features are: an increased erythrocyte sedimentation rate, hyperglobulinemia, and the presence in the serum of a macroglobulin of high molecular weight which can be demonstrated by ultra-centrifugation. There may also be weakness, anemia, mucosal hemorrhages and skin ecchymoses, generalised swelling of lymph nodes, hepatosplenomegaly and, in most cases, infiltration of the bone marrow by lymphoid and plasma cells. In some of the cases cryoglobulins were found and jellification of the blood was noted at room temperature.

Since Waldenström described the first patient, about fifty cases have been described, mostly from Continental Europe [1–16,40,41,43]; four cases have been described in the United States [17,23,26], two in England [8,27] and one in Canada [38]. This case is the first from Israel and is of interest because of the finding of "grape cells" in the bone marrow in addition to the typical infiltration of the marrow with lymphoid cells.

## CASE REPORT

A fifty-four year old woman was admitted to the Rothschild Hadassah University Hospital in October 1956 because of increasing weakness, vertigo, headaches and hypertension. In 1943 she had suffered from metrorrhagia which was attributed to an atypical hydatidiform mole. At the same time a right-sided pleural effusion developed. Although no confirmatory evidence of malignancy was found, she received radium therapy as though she had had a chorion-epithelioma. Since then she had been under constant supervision. Repeat chest roentgenograms and Aschheim-Zondek tests have been normal.

The present illness began several months before her admission to our hospital, when she noted swelling of the lymph nodes in her groins; her physician attributed this to a superficial thrombophlebitis secondary to varicose veins. At the same time she began to experience increasing weakness, dyspnoea on effort, vertigo and headaches. Her appetite decreased and

she lost weight. She noticed blue discoloration of the skin without precipitating trauma.

On admission, physical examination revealed a well nourished, pale woman. A large ecchymosis (7 cm. X 4 cm.) was seen on her right arm and a smaller one (3 cm. × 2 cm.) on her left thigh. Enlarged, nontender lymph nodes were found in the axillae and groins. The pupils showed anisocoria and reacted sluggishly to light. The pulse was regular. The area of cardiac dullness as found by percussion was uniformly increased. On auscultation, accentuation of the second aortic sound and a grade 3 systolic murmur were heard over the apex and Erb's point. The blood pressure was 210/100 mm. Hg. Over the bases of both lungs there was dullness to percussion, and on auscultation numerous râles were found. The liver was enlarged 3 to 4 cm. below the costal margin. The spleen could not be felt on admission but became palpable one month later. Her legs were slightly swollen. The patellar reflexes were absent. Funduscopic examination revealed normal discs, constriction of arteries with arteriovenous compression, and small superficial hemorrhages. No exudates were seen.

The erythrocyte sedimentation rate was 130 to 140 mm. in the first hour (Westergren) and persisted at about this level during the patient's two months' stay in the hospital. The urinalysis was normal. The hemoglobin was 9.2 gm. per cent; red blood cells 3,560,000 per cu. mm.; white blood cells, 9,000 per cu. mm. with a differential count of 79 per cent neutrophils, 16 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The thrombocyte count was 171,000 per cu. mm. The blood urea was 41 mg. per cent; glucose, 98 mg. per cent; and cholesterol, 251 mg. per cent. The cephalin-cholesterol flocculation test was 1 plus; the Weltmann coagulation band, 6; total serum proteins, 7.5 gm. per cent with 3.2 gm. per cent albumin and 4.3 gm. per cent globulin. The euglobulins were increased. No cryoglobulins were found. An electrophoretic analysis of the patient's serum by the Tiselius moving boundary method (barbital buffer, pH 8.6, ionic strength 0.1) gave the following results: (Fig. 1A) albumin, 40.5 per cent; α1 globulin, 6.1 per cent; α2 globulin, 17.8 per cent;  $\beta$  globulin, 10.5 per cent; and  $\gamma$  globulin, 25.1 per cent. A marked heterogeneity of the γ complex was observed after a prolonged run. (Fig. 1B.) The Wassermann reaction was 4 plus in

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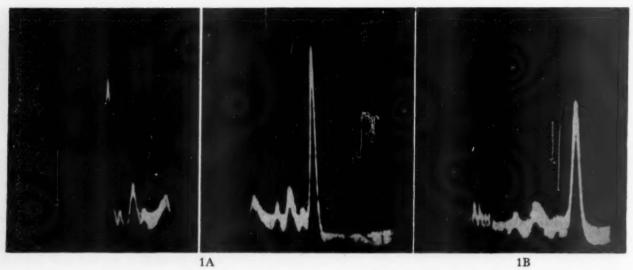


Fig. 1. Moving boundary electrophoresis of patient's serum (barbital buffer, pH 8.6; ionic strength, 0.1; temperature, 1°c.): (a) after running sixty minutes, (b) after running one hundred minutes.

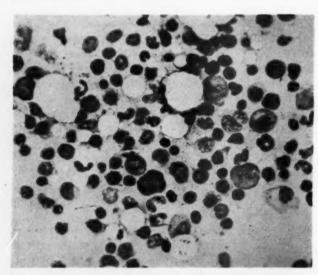


Fig. 2. Bone marrow aspiration, showing predominance of lymphoid cells. (M. G. G. stain.) Original magnification, × 500.

the blood but negative in the cerebrospinal fluid. In the absence of a history of syphilis and because of the presence of hyperglobulinemia, a treponema immobilisation test was performed, which was negative.

Coagulation studies gave the following results: Rumpel-Leede test, negative; coagulation time (Lee-White), 7 to 8 minutes; bleeding time, 6.5 minutes, 7 minutes and 12 minutes on three different occasions; clot retraction, 45 minutes; plasma fibrinogen content, 396 mg. per cent. The plasma prothrombin content was 40 per cent and did not improve after intravenous vitamin K injections. The serum prothrombin content was 3 per cent (Quick). Factors v and vii of Owren and Koller and a thromboplastin generation test [44] were normal.

A bone marrow aspiration taken from the spine re-

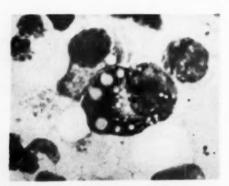


Fig. 3. Grape cell. Original magnification, × 1,000.

vealed a hypercellularity, with normal myeloid and increased erythroid series. A proliferation of lymphoid cells and a slight hyperplasia of plasma cells were noted. (Fig. 2.) Plasma cells were seen which contained cytoplasmic polyhedral and globular bodies. (Figs. 3 and 4.) These bodies took a positive stain with the periodic acid-Schiff reagent, indicating the presence of a mucoprotein [45]. (Fig. 5.) Because of this, the concentration of the serum mucoproteins was determined and was found to be 106 mg. per cent, whereas the normal range for women is 40 to 70 mg. per cent [46].

X-ray of the chest revealed an enlarged heart and small effusions at both lung bases, congestion of the pulmonary circulation and increased hilar shadows. A radiographic bone survey disclosed hyperostosis frontalis interna of the skull and osteoporosis of the vertebral column. An intravenous pyelogram revealed a non-functioning right kidney.

Ultracentrifugation of the patient's serum, performed at the Weizmann Institute of Science, Rehovoth, demonstrated a macroglobulin with a sedimentation constant of 11.7 S, equivalent to a molecular weight of approximately 400,000. Im-

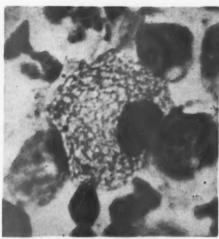
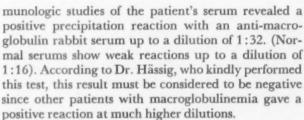


Fig. 4. Crystal-like inclusions in a plasmocytoid reticulum cell. Original magnification, X 1,000.



Since the dominant picture was one of congestive heart failure, the patient was given a salt-poor diet and digitalis. Although her heart failure improved, she still complained of weakness. The anemia did not respond to iron, liver extract and vitamin B<sub>12</sub> therapy and the hypertension did not respond to hydergine, reserpine and ansolysen® therapy. The patient was discharged to her home after two months of hospitalisation, but was readmitted a fortnight later because of a bronchopneumonia and severe heart failure, which was successfully treated with achromycin® and digitalis. She still has a low grade fever which does not respond to any antibiotic.

#### COMMENTS

Waldenström's macroglobulinemia usually occurs in men fifty to seventy years of age but women and young people have been found to be affected. The patients usually consult the physician because of weakness, lassitude, dyspnoea on exertion, bleeding after a tooth extraction, or epistaxis. Occasionally, deterioration of vision due to retinal hemorrhages is the main symptom [8,10]. Many of the patients have been under observation for years because of a markedly increased sedimentation rate [7]. Anemia may be severe, slight or absent. The white blood count is usually normal but occasionally leukocytosis or leukopenia is found. The differential count may be normal; often there is an

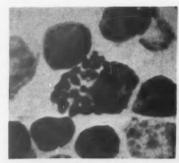


Fig. 5. Grape cell. Positive stain with periodic acid-Schiff. Original magnification, X 1,000.

absolute or relative lymphocytosis [8]. Layani [9] described monocytosis with many Rieder cells. The lymph nodes are enlarged and in most cases hepatosplenomegaly is present [7]. Neurological signs in the form of radiculitis, myelitis and encephalitis have been reported [10–12]. Bone pains are not a feature of the disease.

The urine is usually normal. In some cases proteins which precipitate at 40°-50°c. but do not redissolve at higher or lower temperatures have been reported [4,5]. Bence Jones proteinuria has also been observed [10,12,27-29].

The x-ray findings are usually normal. In some cases osteoporosis has been described [2,5,11] but since most patients are above the age of fifty this is probably of no significance. Pathologic fractures have been reported [2,9]. Hörner [14] found a lymphatic tumor in the mandible and osteoplastic and osteoclastic foci in the left humerus of a young man with macroglobulinemia.

The bone marrow may be normal [2] but often there is an infiltration with lymphoid cells and more rarely with plasma cells. Schaub [5], by serial bone marrow aspirations, demonstrated the transformation of the marrow from a lymphoid cell infiltration early in the disease to a predominance of plasma cells in the later stages. Tischendorf et al. [11] found an increased number of mast cells. In our case, apart from the lymphoid proliferation, we noticed an increased number of plasma cells. In the cytoplasm of some of these cells, globular inclusions or polyhedral bodies were found. These inclusions took the periodic acid-Schiff (PAS) stain, indicating the presence of a mucoprotein. Since in macroglobulinemia there is an increased blood content of glycoproteins [15-17, 47] the presence of an intracellular mucoprotein may be of interest as this may point to a mechanism of absorption or production of glycoproteins within

the cell. Cells with globular inclusions have been called "grape cells" [20] and have been described in multiple myeloma [18–20] and in hyperglobulinemia of non-myelomatous origin [21].

Hemorrhagic phenomena occurred in twothirds of the cases reported [7]. Their cause is not yet clear. In most of the cases with hemorrhagic phenomena, the number of thrombocytes was within normal limits and none of the different plasma clotting factors were deficient. This led some authors to attribute the hemorrhagic phenomena to an increased fragility and permeability of the capillary wall caused by the abnormal proteins [1,4,22]. In other cases a decreased prothrombin and fibringen content of plasma or a decreased prothrombin and accelerator globulin was noted [23,13,17]. Abnormality of the fibrinogen has been described [17]. Thrombocytopenia has also been reported [26]. In one case it was demonstrated that the macroglobulin had an action similar to that of an antiproconvertin and an antiproaccelerin [37]. In our case the bleeding time was prolonged and the prothrombin content of the plasma was decreased.

The electrophoretic pattern of serums from patients with macroglobulinemia is similar to that found in multiple myeloma. There is a sharp, tall peak which usually has the mobility of  $\gamma$  globulins, sometimes that of M globulin, and less frequently that of  $\beta$  globulin [17]. The Tiselius electrophoretogram of the serum of our patient revealed an increase in the  $\alpha_2$ fraction in the form of a sharp peak and an increase in the  $\gamma$  fraction in which several peaks were present, indicating the presence of several  $\gamma$ globulins of different mobilities. The characteristic sharp, tall peak of multiple myeloma, which is often found in macroglobulinemia, was absent. In this respect our case resembles case No. 1 of Mackay et al. [26].

Ultracentrifugation usually reveals a globulin with a high sedimentation constant, 19 to 20 S [1-4]. Lower sedimentation constants of 13 S and 12.7 S have, however, been described in macroglobulinemia [9,23]. In our patient the sedimentation constant was 11.7 S, which is far above the normal values of 4.5 S for albumin and 7.0 S for  $\gamma$  globulin. It is of interest to note that sedimentation constants of 9.5, 11 and 20 S have been described in cases of  $\alpha$  and  $\beta$  myeloma [32,34]. In  $\gamma$  myeloma no macroglobulins were found [33].

Our patient, like that of Long et al. [38], gave

a biologically false positive reaction for syphilis. Biologically false positive reactions are of two types, acute and chronic [30,31]. The acute biologically false positive reaction occurs during or shortly after a wide variety of non-syphilitic diseases such as atypical pneumonia, malaria, infectious hepatitis, measles, relapsing fever, typhus, etc. It disappears spontaneously within a few days, weeks or months. The chronic biologically false positive reaction is found in leprosy, lupus erythematosus, periarteritis nodosa, rheumatoid arthritis and sarcoidosis, to cite only a few examples. It persists for years and sometimes through life. In many of these patients the sedimentation rate is accelerated and the globulins are increased. Macroglobulinemia, which presents an extremely accelerated sedimentation rate and a hyperglobulinemia, may be added to the long list of causes of chronic biologically false positive reactions, the exact nature of which is not as yet clear.

Ultracentrifugation is still the only means by which a diagnosis of macroglobulinemia can be confirmed. However, Habich and Hässig [35,36] succeeded in sensitizing rabbits with serum from patients with Waldenström's macroglobulinemia, and the antiserum thus produced precipitated serums from patients with Waldenström's macroglobulinemia but not serums from other patients. The antigenic specificity of the macroglobulins was thus proved. Habich [37] found that fourteen of sixteen serums from patients with Waldenström's macroglobulinemia reacted positively with the specific antiserum. Since macroglobulins have also been found in congenital syphilis [37], hepatic cirrhosis and nephrosis [24,25], Kanzow et al. [42] attempted to precipitate the macroglobulins of these serums with the specific antiserum but without success; however, serums from twenty patients with Waldenström's macroglobulinemia were precipitated.

In our patient, the antimacroglobulin precipitation test was negative, due possibly to the difference in the molecular weight of the macroglobulins in our case [11.7 S] and the molecular weight of the macroglobulins with which the antiserum was prepared (15 to 25 S). Schulten et al. [7], who performed the antimacroglobulin precipitation test in four cases of macroglobulinemia with low sedimentation constants, obtained only two positive results.

Diagnosis and Differential Diagnosis. Macroglobulinemia should be suspected in elderly

people who complain of weakness and who do not present other abnormal signs except an increased erythrocyte sedimentation rate accompanied by hyperglobulinemia. Hemorrhagic diathesis, so often found in macroglobulinemia, hepatosplenomegaly and enlarged lymph nodes may be absent. A bone marrow smear showing a lymphoid infiltration of the marrow, and an abnormal electrophoretogram of the serum proteins should suggest the diagnosis. Confirmation can be achieved by the antimacroglobulin precipitation test, which is positive in the majority of cases. Final proof is established only by ultracentrifugation.

The differential diagnosis of macroglobulinemia should include chronic lymphatic leukemia, as both these diseases may present with enlarged lymph nodes, hepatosplenomegaly and infiltration of the bone marrow with lymphocytes. They can, however, be distinguished electrophoretically by the presence of abnormal proteins in the serum of macroglobulinemia which are not found in chronic lymphatic leukemia [39]. Macroglobulinemia should also be differentiated from multiple myeloma, as both show a similar electrophoretic pattern of the serum proteins, and macroglobulinemia may occasionally present a predominance of plasma cells in the bone marrow. However, bone pains and the characteristic x-ray picture of multiple myeloma are absent in macroglobulinemia. Macroglobulins may occur in the serums of patients with multiple myeloma.

The etiology and pathogenesis of macroglobulinemia are unknown. The lymphoid cell infiltration of the bone marrow in macroglobulinemia probably produces the macroglobulins in the same way that the plasma cells of multiple myeloma produce myeloma proteins. The finding of Bence Jones proteinuria in both diseases and the predominance of plasma cells in some cases of macroglobulinemia indicate a relationship. The occurrence in macroglobulinemia of macroglobulins with low sedimentation constants, and in multiple myeloma of myeloma proteins with high sedimentation constants may point to the existence of transition forms between these two diseases. They both have a poor prognosis.

#### SUMMARY

A case of macroglobulinemia is reported in which plasma cells containing a glycoprotein were present in the bone marrow.

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## Organic Phosphate Insecticide Poisoning\*

#### Residual Effects in Two Cases

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The prevailing opinion is that human intoxication with the organic phosphate insecticides is an all-or-none affair; that once the acute phase of the poisoning is over (if death does not result), the patient will recover completely. True, some weeks may pass prior to the recovery of normal blood cholinesterase levels in the poisoned individual, but the implication is that no residual symptoms will be noted [1].

In certain animals exposure to some of the anticholinesterase organic phosphates may result in peripheral nerve damage. The chicken appears to be unusually prone to the development of such peripheral nerve damage and has been extensively used in experiments. Various organic phosphates (DFP, isopestox®, EPN and TOCP) have been found to produce paralysis in the chicken. The best single reference to this type of experimental work is the article by Durham et al. [2]. It has been established that actual demyelination is present in some of the damaged nerves [2-4], in paralysis produced in the chicken by these organic phosphates.

Parallel experience in the human is nearly non-existent. Petry in 1951 [5] reported the case of a greenhouse worker who used parathion in closed hot-houses ten or twelve times during a period of four weeks. He did not wear a mask. After each application the symptoms of acute organic phosphate intoxication developed. Four months after the last application the patient noted the onset of giddiness and weakness of the legs. Later, paralysis of muscles of the upper and lower extremities ensued. Two years later the peroneal muscles were still paralyzed, he experienced difficulty in walking and complained of loss of memory, inability to concentrate, and impotence. Bidstrup et al. [6,7] in 1953 and 1954 reported on a group of three chemical plant workers employed in a plant manufacturing isopestox (mipafox), in whom the symptoms of acute organic phosphate poisoning developed. They were treated with atropine, which resulted in prompt amelioration of symptoms. However, two of three workers had weakness of the muscles of the legs. In one, this amounted to nearly complete paralysis of the leg muscles; she also had similar, although less severe, involvement of the muscles of the forearms. After ten months both persons still had residual effects. Two years after the initial symptoms the more severely affected individual was unable to walk as a result of paralysis of the leg muscles.

Triorthocresyl phosphate (TOCP) has been the cause of paralysis in man in cases of ingestion of certain beverages containing Jamaica ginger. TOCP was found in batches of this ginger and was proved to be the agent responsible for the cases of paralysis [8,9]. Smith and Lillie [10] in 1931 first showed that demyelination was involved in the affected nerves, but only at a much later date was it noted that TOCP was an active anticholinesterase agent [11]. Cases of paralysis due to TOCP still occur. The latest report is by Glasson and Stelling [12], 1956.

In the course of studying cases of organic phosphate insecticide poisoning in man, two cases of apparent nerve damage following the acute intoxication have been noted. These are recorded in as much detail as can be gathered. I realize that certain loopholes exist in the recorded data. However, in view of the increasing use of the organic phosphate insecticides, similar cases may be encountered. The purpose of reporting these cases, incomplete as they may be, is to alert others to the possibility of peripheral nerve damage as a result of exposure to the highly toxic organic phosphates.

#### CASE REPORTS

CASE I. A forty-four year old white man, was employed in an experimental agriculture station. In the 1940's he experienced a febrile illness which was

\* This work was carried out under Army Chemical Corps Contract DA-18-108-CML-5473.

diagnosed as undulant fever. Following several months of a low grade fever, the patient was well until 1952. Except for this, and acute appendicitis, there was no pertinent past history. In the spring of 1952 an experimental insecticide project commenced in which this man took an active part. This project consisted of spraying trees and plants with various insecticides including parathion, EPN, DDT, dieldrin and lead arsenate. This man helped mix the solutions, supervised the spraying operation, and inspected the plants following spraying to determine the effects of the insecticides upon the insect population. No particular precautions were taken to prevent exposure to the insecticides. In April, 1952, approximately one month after the experimental project was initiated, he began to experience headaches, nausea, generalized aches, pains and malaise. Because of marked pain in the abdomen and flank, cystoscopy was undertaken which revealed a normal urinary bladder and outflow tract. In June, 1952, approximately three months following the beginning of the spraying project, an exploratory laparotomy was performed because of marked persistent abdominal pain. No cause of the abdominal pain was found. However, the patient left the hospital markedly improved. He returned to work but during the fall and winter he had no contact with insecticides. He noted the onset of mild jaundice in the fall, which cleared by the following spring.

The experimental insecticide program recommenced about March, 1953. Again, symptoms of abdominal cramping, malaise, nausea and loss of appetite with weight loss were noted. In the late spring jaundice developed again, and because of this and the other symptoms a second exploratory laparotomy was undertaken in June, 1953. A cholecystectomy was carried out with exploration of the common bile duct. No cause for the jaundice was noted and the liver appeared normal. Following the operative procedure the jaundice cleared, but after returning to work in August, 1953, his abdominal cramps returned. During the late fall and winter he did not come in contact with the insecticides and he

felt much better.

In the spring of 1954 the project was once again resumed. Shortly thereafter he began to experience symptoms similar to those noted during the preceding two spring seasons. Also noted were nervousness and difficulty maintaining balance, with some staggering upon walking. Insomnia was a particularly prominent symptom. On a Sunday in May 1954, the patient's family returned home from church to find him on the floor unconscious. He was treated by a physician first on an emergency basis at home, then in a hospital for organic phosphate poisoning. He responded well to atropine and regained consciousness after several hours. During his hospitalization he was extremely weak, had difficulty at first in moving his extremities, and complained of a lack of sensation in the hands and feet, and paresthesias of the extremities. Tinnitus

appeared during his hospital stay and there was a marked disturbance of equilibrium. Blood cholinesterase levels were determined at the time of the acute attack. Plasma cholinesterase was 34 per cent, and red blood cell cholinesterase 37 per cent of normal. Approximately two weeks later the plasma level was 100 per cent and the red blood cell level 75 per cent of normal. One month after the first cholinesterase determination the plasma level was 206 per cent and the red blood cell level was 85 per cent of normal. At no time was there evidence of heavy metal poisoning, and stippling of the erythrocytes was never noted.

Despite the expected return to normal of the blood cholinesterase level, the patient continued to experience weakness, malaise, great fatiguability, insomnia, disturbance of equilibrium, tinnitus and other symptoms. Although the symptoms have varied in severity, they have persisted up to the time of the most recent physical examination in September, 1956, with no noticeable true amelioration. At the time of this examination the patient was found to be thin, and there was a slight tremor of the outstretched hands. The deep tendon reflexes were hyperactive. No pathologic reflexes were found. Some lack of coordination was noted; in particular, finger-to-nose movement was not quite accurately performed. There was no other abnormality on physical examination or on detailed neurologic examination. Hearing was not tested, but an audiogram taken eight months previously, in January, 1956, revealed nerve type deafness of a flat type averaging 36 per cent loss in the right ear and 37 per cent loss in the left ear. Electroencephalogram

During the more than two years that have elapsed since the acute organic phosphate intoxication of May, 1954, the patient has constantly had the symptoms noted. He has been examined by numerous well qualified physicians whose findings have been in essential agreement. There has been no known exposure to organic phosphate insecticides since the acute exposure of 1954. Indeed, following a year's leave of absence from his position, the patient felt too unwell to continue work in his former position and has been unable to work at any job for more than twenty-five hours a week. Blood cholinesterase levels performed in the fall of 1956 were normal on three occasions.

CASE II. In 1944, a forty-four year old white, practicing physician, began spending every Sunday working on his large lawn and garden during the entire day. A great deal of time was spent in applying insecticides to the lawn and shrubbery. In the initial phase of his amateur gardening various insecticides were tried, DDT being the predominant active agent. About September, 1954, the patient first began using malathion. This proved to be extremely effective against the insect population and the patient soon abandoned every other insecticide. Malathion was sprayed on the lawn and garden with a "hose-on"

attachment to the regular garden hose. The 6 per cent malathion preparation was mixed in the "hoseon" jar and the patient used his bare hand to close the jar when inverting it. He dressed in shorts and sneakers and was often thoroughly soaked with the spray after application. The malathion spray was applied weekly and the patient's first symptoms appeared several months after beginning this spraying program. The symptomatology was vague at first and consisted of a sensation of tiredness and irritability which was noticed by his family as much as the patient himself. He often took Sunday dinners alone because of his extreme irritability. Weakness and some paresthesias of the face and oral cavity were also noticed. In the early spring of 1955 the patient began using 50 per cent malathion in a hand sprayer, spraying plants both in the yard and plants in the open sun area of the living room of the house. Symptomatology was marked by April, 1955. Weakness was generalized. Tremor had developed. Headaches and difficulty in focusing the eyes were prominent. The muscles of the lower leg and the right shoulder girdle were extremely weak. He had some loss of equilibrium and tinnitus. He collapsed with marked prostration in June, 1955, and was immediately hospitalized. During an eighteen-day hospital stay the patient gradually improved with the exception of muscle weakness in the right shoulder girdle and peroneal groups. Repeated examinations revealed only some decrease in sensation of the right side of the face, unsteadiness of gait, slight winging of the right scapula and weakness of the peroneal muscles. The cerebrospinal fluid was normal in all respects. The hemogram was normal and blood chemistries including protein-bound iodine, cholesterol, alkaline and acid phosphatase, calcium, total serum protein, albumin and globulin were normal. Electrocardiogram and x-rays of skull and chest were

Following discharge from the hospital the patient felt much improved, although generalized weakness and particular weakness in the right shoulder girdle, right serratus anterior and both peroneal muscle groups continued. There was some persistence of parasthesias of the right face and oral cavity and some disturbance in sensation in the same region. A subcutaneous fat biopsy was undertaken, and 23 p.p.m. of DDT plus a high level of total organic chloride was found. The patient restricted his work in the yard and garden and avoided contact with insecticides. I last contacted him in September, 1956, more than one year following his collapse with symptoms of acute organic phosphate intoxication. At that time he was finding active practice extremely difficult to carry out even on a part time basis because of fatigability, marked weakness of the muscle groups previously mentioned (especially the left peroneals and right serratus anterior), anorexia and marked weight loss. There is no evidence that this patient had any exposure to heavy metals.

COMMENTS

The similarity of the two cases reported herein is apparent. Both patients had repeated exposures to insecticides of various types. The symptomatology of both was consistent with intoxication with the organic phosphate type of insecticide, and repeated exposure to an organic phosphate was documented in each case, EPN and parathion in the first case, malathion in the second. Blood cholinesterase level depression was proof of organic phosphate poisoning in the first case; no such confirmatory evidence is available in the second case.

Both patients have what appears to be permanent damage. The eighth cranial nerve was damaged in the first patient (both vestibular and cochlear components) and certain peripheral nerves (long thoracic and peroneal nerves) in the second patient. Some sensory and other motor nerves were transiently affected in both patients. In the first patient there was a twentyseven-month period between the acute intoxication and the last physical examination which still revealed residua. In the second patient fifteen months elapsed from acute symptomatology to the last physical examination which revealed continuing nerve damage. At the time of the last physical examination in each instance there was no evidence that recovery would ensue.

The fact is not denied that there may be no cause and effect relationship between the repeated organic phosphate intoxication, with at least one episode of severe poisoning requiring hospitalization, and the peripheral or cranial nerve damage. However, repeated examinations and interviews by well qualified medical personnel have failed to reveal any possible etiological agent or mechanism other than the exposures to the insecticides. It is entirely possible that exposure to the particular combination of insecticides gave rise to the symptomatology and nerve damage. This possibility is a loophole in the cases presented here. In Case II there is evidence of a considerable concentration of DDT and organic chlorides in the body fat, but in the light of the work carried out by Laug et al. [13] and elaborated upon by Hayes et al. [14], there is no reason to suspect that the DDT concentration would indicate chronic poisoning with that agent, and that the symptoms and nerve damage were due to DDT. Perhaps a synergism exists between some of the organic phosphates

and some of the other insecticides, which may account for the permanent damage noted in these two patients. There are no data to support this theory, although one organic phosphate may potentiate another member of the same group [15]. In view of animal and other limited human experience, and in the absence of proof to the contrary, it would seem logical to implicate the organic phosphorus compounds as the toxic agents in the two cases presented.

#### SUMMARY

Two human cases of permanent nerve damage (with attendant muscle, auditory and vestibular dysfunction) and weakness, easy fatigability and weight loss are reported. The patients were both exposed on multiple occasions to certain of the organic phosphate insecticides, and the symptoms of nerve damage began at the time of severe acute exposure to these toxic agents.

These cases are compared to animal studies and other experiences in man when exposure to organic phosphates has resulted in permanent nerve damage.

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# Chronic Pulmonary Insufficiency Secondary to Silo-Filler's Disease\*

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A RECENTLY published report by Lowry and Schuman [1] emphasized that chronic pulmonary disease due to inhalation of silage fumes might in the future be recognized. We believe the following case report represents such an example.

#### CASE REPORT

Patient D. C. (No. 222142). A twenty-eight year old white man was admitted to Wayne County General Hospital on March 3, 1957 with a chief complaint of "smothering and headaches." The patient dated the onset of his illness as four days prior to admission when chills and fever developed. He saw a physician and was given cold pills. On the following day, headache and dyspnea developed which persisted until the day before admission when he began to feel less ill. A cough productive of whitish material accompanied this episode. There was no history of chest pain, hemoptysis, night sweats, weight loss or exposure to birds or rabbits. He stated that two of his children were ill at home with severe "colds."

Past history revealed that the patient had pertussis and rubeola at six months of age. He recovered from these infections without known sequelae, and was in good health until age thirteen when he had pneumonia for three weeks. On recovery from this illness, he felt perfectly well. He left school after finishing the seventh grade to do farm work; in September 1954 he was told to enter a silo and "level it off."

This silo was approximately 30 feet high and 12 feet in diameter, and had been almost completely filled the previous day with straight corn silage without any added material. Upon opening the door to the silo chute, he immediately noticed intense heat, his eyes and nose burned, and he "felt choked." He saw no red or yellow fumes. He climbed to the top of the silo in this enclosed ladderway in about two minutes, although he felt short of breath and was coughing. He was too weakened to begin work immediately, so he opened a door leading to a platform outside the silo

and rested in the fresh air. He had never had any difficulty ensiling before, although he had heard of illness following entrance into silos recently filled with corn.

Subsequently, he reentered the silo proper, performed his job in about five minutes, and then chose to return to the ground via an unenclosed ladder on the side of the silo. That afternoon he felt "smothered," nauseated and feverish, and that night he took to bed for a week. He had an illness characterized by malaise, weakness, headache, chest pain, fever, anorexia, chilliness, dyspnea on very slight exertion, and cough moderately productive of white sputum. He was attended by a physician who stated he had "flu" and treated him with injections. Because of the persistence of this disease, a chest x-ray was obtained to rule out tuberculosis; the patient was informed that the x-ray was "negative."

The patient remained acutely ill for three weeks, but stated he felt too tired to do any work at all that winter. When he did resume farm work in March 1955, he noticed that he was very short of breath on mild exertion. Subsequently, he came to Detroit to find assembly work which would be less strenuous. However, a febrile illness developed and he was admitted to a sanitarium as a tuberculosis suspect. He was evaluated there from December 21, 1955 to January 12, 1956 and was discharged with a diagnosis of bronchopneumonia. It was stated that he was not considered a tuberculosis case in their records. A chest x-ray taken at that hospital two weeks after discharge showed partial blunting of both costophrenic angles and slight strand-like fibrosis at the first and second interspaces on the left.

In the spring of 1956, the patient returned to Ohio to attempt farming once more. Again he found that the exertion entailed made him so short of breath that he could not continue such work; that winter he resumed his old job in Detroit.

The patient smoked ten to twenty cigarettes daily. There was no finding of hay fever, asthma or allergy in either his personal or family history.

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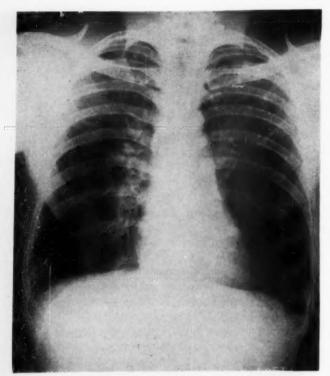


Fig. 1. Posteroanterior projection showing accentuated bronchovascular markings in upper portions of both lung fields.

Physical examination on admission revealed a well developed, well nourished white man in moderate respiratory distress with slight peripheral cyanosis. Weight was 122 pounds; height, 5 feet 4 inches; oral temperature, 102°F.; respiratory rate, 25 per minute; pulse rate, 100 per minute; blood pressure, 100/60 mm. Hg. The skin was warm and moist with normal turgor; an acneiform eruption was present on the back and shoulders. The eyes, ears, nose and throat appeared normal; the teeth were carious. The chest was symmetrical with equal expansions bilaterally. Inspiratory and expiratory moist rales, and scattered expiratory wheezes were heard throughout both lung fields; vocal and tactile fremitus as well as percussion note were normal. There was no cardiomegaly noted. Regular sinus rhythm was present; A2 was louder than P2, and no murmurs were heard. The rest of the physical examination was within normal limits; none of the examiners thought that clubbing of the fingers was

A chest film taken on admission (Fig. 1) showed that the bronchovascular markings in the upper portions of both lung fields were accentuated, but there was no evidence of active parenchymal inflammatory disease. The heart was not enlarged, and its contour was normal. An electrocardiogram was within normal limits. The leukocyte count was 8,250 per cu. mm.; sedimentation rate 34 mm. per hour (Wintrobe); hemoglobin 16.3 gm. per 100 cc.; hematocrit, 45 per cent; and the erythrocyte count, 4,740,000 per cu. mm. On admission, the carbon dioxide combining

power was 30 mEq./L.; three weeks later it was 27 mEq./L. Sputum culture revealed predominately Hemophilus influenzae and Neisseria. Two blood cultures were sterile; and smears of concentrated sputum for acid-fast bacilli were negative, as were cultures at six weeks. Fasting blood sugar was 66 mg. per cent and blood urea nitrogen 16.1 mg. per cent.

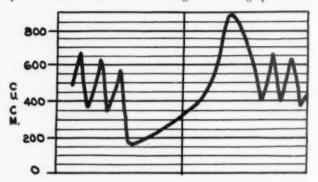


Fig. 2. Vital capacity curve, March 4, 1957. Note the markedly impaired vital capacity with prolonged expiratory effort. Time interval between the vertical lines of graph is twelve seconds.

Total serum proteins were 4.8 gm. per cent with albumin 2.7 gm. per cent and globulin 2.1 gm. per cent. Cold agglutinins were positive 1:16 initially and 1:32 in three weeks. Skin tests with old tuberculin 1:1000, blastomycin, coccidioidin and histoplasmin were negative at forty-eight and seventy-two hours. Urinalysis was not abnormal.

The clinical impression was that the patient had chronic pulmonary insufficiency secondary to inhalation of oxides of nitrogen with a superimposed acute bronchiolitis. He became afebrile on the day of admission following treatment with penicillin, streptomycin, expectorants, bronchodilators and antihistamines. The next day positive pressure oxygen inhalations with nebulization of aerolone® were added to the above regimen. Pulmonary function studies were obtained on the second hospital day demonstrating a vital capacity (Fig. 2) of 1,450 cc., 36.2 per cent of the predicted normal value. The maximum breathing capacity was 21 L., 17 per cent of normal. In three seconds, the patient could exhale 69 per cent of his vital capacity.

Although the patient improved rapidly, he continued raising 30 to 40 cc. of yellowish mucoid sputum daily and rales persisted at both lung bases after a week of treatment. His antimicrobial therapy was changed to chloramphenicol and sulfisoxazole. On discharge twenty-two days after admission coarse moist rales were still present in the left lung base. A chest x-ray taken on the day before discharge revealed no change from the initial film. Vital capacity (Fig. 3) after fifteen days of treatment was 2,343 cc., 58 per cent of predicted normal, with 94 per cent being exhaled in three seconds. The maximum breathing capacity was 37.7 L. or 30.4 per cent of predicted normal.

TABLE I SUMMARY OF FINDINGS

Studies	Patient	Normal
Lung volumes:		
Vital capacity	2130 cc. BTPS	4030 cc. BTPS
Residual volume	3305 cc. BTPS	1454 cc. BTPS
Distribution of ventilation:		
Nitrogen rise over 500 cc. of expiration	3.8%	Less than 1.5%
Diffusion (CO method):		
Steady state	16.9 ml./mm. Hg/min.	13-20 ml./mm. Hg/min.
Single breath	29.0 ml./mm. Hg/min.	17-40 ml./mm. Hg/min.
Mechanics of breathing:		
Compliance of lungs	0.062 L./cm. H <sub>2</sub> O	0.200 L./cm. H <sub>2</sub> O
Maximum breathing capacity	47.2 L./min.	124 L./min.
Timed vital capacity		
1 second	64.7%	83%
3 seconds	90.5%	100%
Arterial blood gases:		
Arterial O <sub>2</sub> saturation	97.4%	96%
pCO <sub>2</sub>	30.1 mm. Hg	40 mm. Hg

Through the courtesy of Dr. Benjamin M. Lewis, assistant professor of medicine at Wayne State University College of Medicine, this patient was studied in the Pulmonary Function Laboratory two weeks following discharge from Wayne County General Hospital. Table 1 is a summary of findings at that time.

Dr. Lewis' interpretation of this data was as follows. "The most striking abnormalities shown are an increase of residual volume, a decrease in maximum breathing capacity, and a slowing of the timed vital capacity. These findings are characteristic of obstructive emphysema, as is the poor distribution of inspired gas. The low value for pulmonary compliance may be attributed to decreased elasticity of the lungs; however, low values for compliance are seen in patients with emphysema during rapid breathing (patient's respiratory rate was 25 per minute). The diffusing capacity of the lungs was within the normal range by both methods used. Arterial oxygen saturation was normal, and the low tension of carbon dioxide is due to hyperventilation during the obtaining of the arterial sample" [4].

#### COMMENTS

The clinical syndrome produced by acute toxicity from exposure to the oxides of nitrogen (primarily nitrogen dioxide) has been thoroughly described. Briefly, it consists of dyspnea, weakness and cough, associated with a choking sensation or inability to breathe deeply, noted during or immediately after exposure to silage

gas. Some victims have noted a yellow-to-brown or red colored gas which had collected above the silage. A latent interval of two to three weeks has been noted [1] in some cases, during which time the symptoms remain stationary or are but slightly progressive.

Following this interval, chills, fever, increasing dyspnea and cyanosis occur leading to death

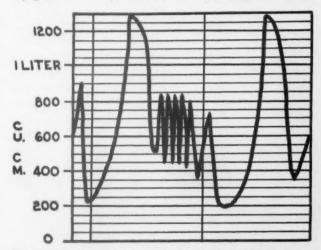


Fig. 3. Vital capacity curve, March 19, 1957. Note the improvement in vital capacity and shortening of time needed for expiration.

within three and one half to six weeks [1]. Autopsy studies have shown pulmonary edema

MARCH, 1958

and bronchopneumonia in those patients dying within a few days of exposure [2,3], and bronchiolitis fibrosa obliterans in patients dying three to four weeks after exposure [1]. Chest x-ray may show patchy areas of pneumonitis or multiple granular to nodular densities of the lung fields which gradually resolve in those patients who recover (Cases 3 and 4 of Lowry and Schuman [1], Case 2 of Delaney et al. [3]).

We believe our patient to be the first reported case in which chronic pulmonary disease ensued as a result of exposure to silage gas. Pulmonary function studies were normal in recovered Case 2 of Delaney et al. Although Cases 3 and 4 of Lowry and Schuman had slight residual nodular densities in the lung fields on x-ray after four to six months, the patients had no symptoms. Since treatment with adrenal cortical steroids effected dramatic relief of symptoms in the latter two patients, it is quite possible that sequelae due to pulmonary bronchiolar fibrosis were prevented.

With respect to our case, several features are of interest.

First, we would like to emphasize that farmers should be duly cautious when in or about a recently filled silo, even when no gas is apparent. In a recent report Grayson [2] has reviewed in detail the physical properties of the oxides of nitrogen and the conditions under which these gases are likely to accumulate, such as drought, high nitrate soils, etc.

Secondly, in our patient we were surprised to find such a disparity between the minimal chest x-ray findings and the markedly impaired pulmonary function tests. However, this might be expected in a diffuse process primarily affecting

the bronchioles of the lung. In addition, the findings of markedly diminished maximum breathing capacity, disproportionately depressed in comparison to the vital capacity, and extremely slow expiratory effort reflected by the timed vital capacity point to diffuse obstructive bronchiolar disease.

Lastly, we believe that the improvement brought about by expectorants, bronchodilators given with intermittent positive pressure, and antimicrobials, is worthy of mention. However, in our case it was apparent that a severe degree of residual impairment in pulmonary function had occurred and was not reversible.

#### SUMMARY

A case of severe chronic pulmonary insufficiency is presented which we believe was caused by exposure to silage gas. This patient in addition had a respiratory infection which precipitated acute respiratory distress. Pulmonary function studies revealed a diffuse bronchiolar obstructive process, which improved somewhat with symptomatic therapy but was largely irreversible.

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## Sjögren's Syndrome\*

# Review of the Literature and Report of a Case with Achalasia of the Esophagus

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ALTHOUGH the concurrence of arthritis and keratoconjunctivitis sicca had been recognized by others previously [1,2], an analysis of thirteen cases manifesting both diseases (with associated lacrimal and salivary gland involvement) associated Sjögren's name [3–14] with their nosologic unity. That the triad of arthritis, keratoconjunctivitis sicca and salivary gland abnormality constitutes a distinct syndrome has since been firmly established [15,16]. Keratoconjunctivitis sicca alone also has been called Sjögren's syndrome but it would seem, by recent consensus, that the triad indicated should be present to make the diagnosis a useful one.

Several series of cases and numerous individual case reports have been recorded [4,7,17-24]. Yet, for the most part the nature of the "arthritis" has always been very much in question. Since many of these cases were reported in the ophthalmological literature, only cursory reference to "an arthritic picture" was made [17,25,26], and only recently has this been correctly diagnosed as true rheumatoid arthritis [27-30].

Incidence. To estimate a true incidence from published reports is impossible. Sjögren's original series cited nineteen patients with keratoconjunctivitis sicca and thirteen patients with arthritis [5,14,24]. This incidence of arthritis in patients with keratoconjunctivitis sicca has been repeatedly confirmed [5,17,21,31]. By 1948 Sjögren had collected data on sixty-two patients with keratoconjunctivitis sicca, forty of whom had arthritis [6]. In 1950 Touraine, using the triad as his criterion, was able to collect data on 101 cases [23]. The incidence of keratoconjunctivitis sicca in all patients with disorders of the eye has been estimated as 1 to 20,000 by

Beetham [32]. Holm [16] found fifty-three patients with keratoconjunctivitis sicca among 440 with rheumatoid arthritis. Thompson and Eadie [27] found 14.3 per cent of 210 patients with rheumatoid arthritis also manifesting keratoconjunctivitis sicca. They reported that fourteen of eighteen patients with keratoconjunctivitis sicca had rheumatoid arthritis. The work of Reader et al. [28], Gifford et al. [17], Bruce [25,33] and others confirms this relationship. Close to 90 per cent of the patients reported on are women [5,14,16,34], many past the menopause. Male patients, however, also are reported [5].

Clinical Picture. The classical clinical picture is presented by a patient with rheumatoid arthritis who complains of blurring of vision, perhaps associated with lack of tearing, a dry mouth and salivary gland enlargement, either parotid or submaxillary [14,35]. Visual or salivary difficulties may antedate the arthritic complaints [36-38]. Parotid enlargement is usually recurrent and self-limited [20,39-41] but is not necessarily bilateral. The glands are sometimes red and swollen, at other times hard and indurated. The arthritis ranges from mild, early rheumatoid arthritis to severe, crippling forms with typical ulnar deviation, subcutaneous nodules and even spondylitis. The lacrimal glands rarely if ever enlarge [27]. There are symptoms of dysphagia [37], cough, and evidences of involvement of the secretory glands of the esophagus and trachea [2,39,40].

Physical examination shows dry mucous membranes, lack of tears, and occasionally a distinctive lesion of the fingernail associated with brownish discoloration [27]. Gastric achlorhydria seems to be present in about sixty per

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cent of reported cases [24,27,31,33,35,36,38,42,43]; an increased incidence of gastric achlorhydria in rheumatoid arthritis had already been demonstrated [44]. Pancreatic secretions are not affected [45]. Renal and pulmonary complica-

tions are reported [39,46].

Three cases of Sjögren's syndrome with Raynaud's disease [33,41,47] have been recorded. There are four cases of Felty's syndrome [30,48], and two cases of scleroderma have been cited [16,49]. While the L.E. cell preparation has been reported positive in only two instances [21,43], a review of older cases would suggest a higher incidence of lupus erythematosus, of which parotitis is a known feature [14,16]. The relationship to Mickulicz's disease has been reviewed by Morgan [21], who believes that the two conditions may well be identical. He reviewed Sjögren's original slides and found histological similarity to his own cases (eighteen) of Mickulicz's disease. In addition, a review of the clinical similarities led him to postulate their identity.

The diagnosis of keratoconjuncti-Diagnosis. vitis sicca is made by the finding of superficial lesions of the cornea on rose bengal staining and by demonstrating diminished lacrimal gland response by means of a Schirmer test [50]. When less than 15 mm. of a thin strip of filter paper placed under the eyelid near the gland is moistened in five minutes the test is considered positive [51,52]. By carrying out this test in sixtytwo patients with rheumatoid arthritis and in sixty-two patients free of this disorder, Reader et al. found a statistically significant difference in the incidence of tear production in their arthritic patients [28], describing many grades of tear gland atrophy.

Salivary production is tested for by a variety of means [53]. Sialography by Ollerenshaw and Rose [54] showed non-filling of acini in twelve cases of Sjögren's syndrome; in one instance the sialogram was so badly distorted as to bear comparison with a Streptococcus viridans sialodochitis. This has been shown by others [55].

Pathology. Reports as to the pathology of the syndrome have come from autopsy and biopsy evidence. Sjögren described the late stage of parotid pathology as consisting of "dense lymphocytic infiltration of the gland parenchyma with atrophy and degeneration of secreting cells" [14]. This, he believed, was similar to the process in the lacrimal gland which led to its eventual atrophy. Yet he considered the earliest

change to be a "granular degeneration of the cytoplasm of the secreting cells which shrink to where they resemble lymphocytes" [7]. Pointing out that Sjögren was actually describing only a disturbance of zymogen granule distribution, Holm found only occasional lymphocytic infiltration in biopsied parotid glands and doubts a specific pathological lesion [16]. However, later investigators have all confirmed the original description of lymphocytic infiltration in advanced cases of the disease [18,21,30,56]. These lymphocyte aggregations have been compared to "lymphorrhages" found in other organs of rheumatoid subjects [28]. Another distinct finding, an "epimyoepithelial island," is described by Morgan who found it not only in his own cases of Mickulicz's disease but also in the case of Ellman et al. and in one of Sjögren's illustrations [21]. Ehrlich and Greenberg [47] report nests of cells in reticular arrangement between the lining epithelium and the basement membrane of the ducts. Most observers state that parotid involvement is uneven-whole lobules are spared, while others show varying degrees of destruction [41,56]. Many normal glands have been described in this disorder [16,18]. Histologic lesions involving the secretory glands of the trachea, pharynx and esophagus are reported [39].

No consistent, hematological finding is characteristic of this disease that is not compatible with rheumatoid arthritis [5]. Electrophoretic examination has not been reported. There are no reports at present as to whether or not the various agglutination reactions for rheumatoid arthritis are demonstrable. Two reports are available as to 17-ketosteroid excretion, one reporting low normal values [49]. Pond [34] examined eleven women with this syndrome and found the 17-ketosteroid excretion to average 2.3 mg./twenty-four hours as compared with the normal range in his laboratory of 4 to 14 mg./twenty-four hours.

Klein [57], in his analysis of precorneal films of patients with keratoconjunctivitis sicca, concluded that these films lacked the normal watery contribution from the lacrimal glands, and thus were more viscous. He also quoted Ridley who found the protein content of tears to be diminished in keratoconjunctivitis sicca.

Etiology. All possible causative agents of disease have been cited at one time or another in connection with the etiology of Sjögren's syndrome. Avitaminosis [22,42,58,59] was first

implicated because of xerophthalmia and xerostomatitis, but failure of vitamin A therapy militated against this etiology [43]. Other vitamin deficiencies have not been convincingly invoked [60]. The autonomic nervous system was next suspected and the eye lesions of facial palsies were mentioned [16,33,55]. Leriche [61] reported relief of ophthalmologic and salivary symptoms in a patient upon whom he performed cervical sympathectomy. Familial occurrence is repeatedly cited. The findings of Cloverdale [26], as well as of Lisch [38] who collected data on twelve cases in three generations of one family, lend weight to this. Sjögren, in citing fourteen cases of congenital alacrimia (five patients with keratoconjunctivitis sicca), suggests that the picture may be one of "a partial symptom of the hereditary ectodermal dysplasia of the anhydrous type" [3]; this phraseology is echoed by others [36]. A viral etiology is possible [62]. Similarity to sarcoidosis has led speculation along that line [60] and, of course, the "collagen diseases" have also been intimately associated with this syndrome [49]. It may be granted that since all glands of the body contain various elements of connective tissue in their stroma they cannot but fail to react, entirely non-specifically, in a systemic disease such as rheumatoid arthritis.

Therapy. With no known etiology, it is not surprising that the current state of therapy is chaotic. While ACTH and cortisone uniformly relieve the associated arthritis, their effect upon lacrimal and salivary secretion is equivocal at best [31,63,64]. Frenkel et al. [51] gave ACTH to the point of hyperadrenalism and they were able to effect some quantitative increase of salivary and lacrimal secretions, but only temporarily. The effectiveness of any therapy is difficult to evaluate because of the variable and, on the whole, benign course of this syndrome. Sympathectomy [61], vitamin therapy [60], estrogens [18,65,66], androgens [36], pituitary implants [60] and x-ray treatment have had their advocates [67]. The surgical blockage of lacrimal outflow offers relief in some cases but the essential pathology remains unaltered. Of course, the arthritis has been treated much as any other type of rheumatoid arthritis.

#### CASE REPORT

A forty-four year old white male roofer (No. 105988), of Hungarian extraction, was admitted to the United States Army Hospital, Fort Dix, with the chief complaint of acute pain and swelling of the

hand, shoulder and elbow joints of one week's duration, and bilateral swelling of the parotid glands of three days' duration.

The patient was first aware of arthritis four years prior to admission when pain and swelling of both elbow joints developed. Since that time he had had chronic and disabling arthritis, involving all of the following joints: knees, hands, proximal interphalangeal joints, distal interphalangeal joints, hips, elbows, shoulders and costosternal articulations, as well as the temporomandibular joints bilaterally. Treatment for this consisted of various proprietary aminopyrine derivatives, as well as intramuscular gold therapy and, recently, cortisone, with only indifferent success. Steroid therapy was cut short because of the Hungarian uprising. Within a few weeks prior to admission his joint symptoms had increased markedly and his hands, shoulders, elbows and sternoclavicular joints had become acutely painful.

Since early in 1950 the patient had begun to notice substernal epigastric distress immediately following meals. Food would get "stuck in his chest," and he gradually had to stop eating heavy meals. This progressed to the point where, in 1955, after taking several pills, complete obstruction occurred and a "muscle-splitting" operation was done in Budapest for a "tightening of the tube to the stomach." He had also in the past year been aware of a lack of tears.

The patient had never had parotid swelling before and he did not remember having mumps as a child. He was not aware of a diminution in the flow of saliva. However, he had had visual difficulties, with occasional blurring of vision and drying of the eyes for several months. He had never had hematemesis, jaundice or melena, and there was no history of pulmonary disease.

The past and family history, as well as systemic review, were completely non-contributory.

Physical examination revealed a thin, asthenic, white man in acute distress because of joint pain, and looking chronically ill. The head was grossly normal. The parotid glands were bilaterally, diffusely enlarged and palpable, giving a pouch-like appearance to the angle of the jaw; they were red and swollen. (Fig. 1.) The mouth showed fissures and cracking of both lips, slight superficial ulcerations of the inner lip margin and marked xerostomatitis. There was slight conjunctival injection, with a few superficial spots on rose-bengal staining of both corneas. Generalized lymphadenopathy, involving the axillary, epitrochlear and inguinal glands, was noted. The thyroid was firm and moderately enlarged. The chest was increased in A-P diameter. The lungs were clear to percussion and auscultation. Examination of the heart showed regular sinus rhythm, no murmurs, rubs, thrills or gallops. No hepatosplenomegaly was noted. Neurologic examination was normal. Interphalangeal joints of both hands were hot and swollen (Fig. 2); both wrists were markedly swollen, with residual



Fig. 1. Bilateral parotitis in a case of Sjögren's syndrome. The glands were so swollen that an admission diagnosis of mumps was considered. This swelling was self-limited.

deformity and slight ulnar deviation, as well as acute heat and redness. The right ankle and both shoulders were hot and painful. The sternoclavicular junctions of ribs 3, 4 and 5 were red and swollen.

The white blood cell count on admission was 9,800 per cu. mm. with 8 juvenile forms, 86 per cent neutrophils, 14 per cent lymphocytes and the hemoglobin 12 gm. per cent with a hematocrit of 42 per cent. The urine was clear, reaction acid, specific gravity 1.025, and contained no protein or sugar. The erythrocyte sedimentation rate on admission was 46 mm./hour (Wintrobe). Serological tests for syphilis were negative. Throat culture showed a scant growth of beta hemolytic streptococci. The serum amylase was 146 units. The antistreptolysin titer was 100 to 150 Todd units. Serum calcium was 9 mg. per cent, inorganic phosphorus 3 mg. per cent and alkaline phosphatase 5.4 Bodansky units. The serum total protein was 5.4 gm. per cent, albumin 3.7 and globulin 1.7. Another determination gave a total protein of 6.2 gm. per cent with paper electrophoresis showing: albumin 51.3, alpha-1-globulin 3.9, alpha-2-globulin 13.7, beta globulin 12.1, gamma globulin 15.5, lipoprotein 3.5, indicative of an increased alpha-1 and alpha-2-globulin as well as a decreased albumin fraction by this method (First Army Area Medical Laboratory). The thymol turbidity test was 2 units. There was no retention of bromsulphalein in forty-five minutes. The serum bilirubin was 0.1 mg. per cent, divided equally between direct and indirect



Fig. 2. The hands in Sjögren's syndrome. The deformities are typical of rheumatoid arthritis. Positive agglutination reactions were demonstrated in this case. (See text.)

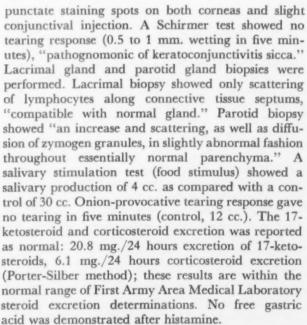
reacting pigments. Coombs' reaction was negative. No ova or parasites were found in the stool and guaiac tests were negative. Three L.E. preparations were negative. The blood urea nitrogen was 14 mg. per cent. The fasting blood sugar was 88 mg. per cent. The reticulocyte count was 0.8 per cent. Repeated tests for C-reactive protein were positive during his hospitalization. Cold hemagglutinins and streptococcus MG agglutinins were not demonstrated.

A routine x-ray of the chest was negative. X-ray films of the hands showed narrowing of the proximal interphalangeal joints and other joint deformities compatible with rheumatoid arthritis of the proximal interphalangeal and metacarpophalangeal articulations of both hands, with secondary osteoarthritic changes. There appeared to be some narrowing of the joint spaces of the left hip, and an incidental finding was radiopaque streaking of both buttocks, probably representing old gold injections. An upper gastrointestinal series showed the esophagus to be constricted at the esophagocardiac junction, with secondary dilatation proximally. At the point of obstruction the esophageal mucosa was smooth and funnel-shaped without irregularities in pattern. (Fig. 3.) Amyl nitrate did not effect passage of barium from the esophagus into the stomach. Five hours after the examination 90 per cent of the barium still remained in the esophagus. An electrocardiogram on admission showed T waves to be diphasic in aVL, inverted in V1, diphasic in V2 and V3. These showed persistent instability but shortly before discharge reverted to normal. This was interpreted as compatible with myocarditis.

The mumps antibody titer was considered normal, in 1:8 dilution, in convalescent serum. Latex fixation test and sheep cell agglutination tests (courtesy of Drs. C. Plotz and J. Singer) were positive for rheumatoid arthritis, in a titer of 1:320. Sheep cell agglutination reactions in the euglobulin titer were positive (1:28) for rheumatoid arthritis, with failure to inhibit in the euglobulin fraction (courtesy of Dr. M. Ziff). An ophthalmology consultant pointed out superficial



Fig. 3A. Frontal view of barium swallow in a case of Sjögren's syndrome. This patient showed achalasia of the esophagus secondary to a stricture at the esophagogastric junction.



On admission the patient's bilateral parotitis was so marked that a diagnosis of mumps was entertained. When severe arthritis was noted the diagnosis of Sjögren's syndrome was made. The patient was given 7.2 gm. of aspirin a day and within three to four days most of his arthritic complaints had gradually subsided. However, the characteristic changes of chronic



Fig. 3B. Lateral view of the esophagus. The mucosa at the point of stricture is normal in contour.

rheumatoid arthritis of both hands persisted. The erythrocyte sedimentation rate remained elevated throughout his hospital course, although very little leukocytosis was evident; the C-reactive protein remained elevated. He was quite comfortable throughout most of his hospitalization but initially complained of dysphagia. This cleared spontaneously within one week. Cortisone eyedrops, 2 per cent instilled into the conjunctivae for six days caused no increase in tearing (0.5 to 1 mm. of wetting in five minutes). It was considered that the patient's arthritis was not severe enough to warrant steroid therapy. Bouginage was contemplated on an outpatient basis for his esophageal difficulties. He was subjectively well one month after diagnosis, suffering only from fleeting arthritic pains.

#### COMMENTS

The case history faithfully fits the criteria for what has been called Sjögren's syndrome. The patient manifested (a) rheumatoid arthritis, (b) keratoconjunctivitis sicca with diminished lacrimal secretions and (c) parotitis with diminished salivary flow. In addition, lack of free acid after histamine stimulation was demonstrated when a tube was placed roent-genographically in his stomach, this precaution was taken because of an esophageal achalasia secondary to a stricture at the gastroesophageal junction. It is impossible to relate satisfactorily

the gastroenterological problem to the patient's primary disease or to rheumatoid arthritis per se. Such a relationship has been mentioned by Richman [68], and pathological lesions of esophagus and stomach were noted by Ellman et al. [39]. Similar lesions are not uncommon in scleroderma. However, there was not the slightest evidence for scleroderma in this case, the patient's skin being completely unaffected. In addition, the agglutination tests for rheumatoid arthritis are rarely positive in scleroderma [65,66].

This appears to be the first case of Sjögren's syndrome in which rheumatoid agglutination activity was demonstrated by two separate and reliable tests [69,70], thus more firmly establishing the diagnosis of true rheumatoid arthritis in these patients. This finding, as well as the electrophoretic demonstration of increased alpha-1 globulin, alpha-2 globulin and lowered albumin levels, awaits confirmation in a large series.

The pathological lesions described in other and perhaps more advanced cases were not present, although the biopsied parotid gland fits the description of Sjögren's early cases. His "fragmented, diffuse cytoplasmic degeneration" accords with the observation in this case of an increased and abnormal scattering of zymogen granules.

More widespread appreciation of this syndrome would serve to establish the true incidence of this variant of rheumatoid arthritis. Perhaps, indeed, an understanding of the elements involved in Sjögren's syndrome, i.e., lacrimal and salivary gland malfunction, lymphocytic infiltration, achlorhydria and the other manifestations would, in turn, cast light on the connective tissue disorder that is rheumatoid disease.

#### SUMMARY

1. The literature concerning Sjögren's syndrome is reviewed as to incidence, clinical findings, pathology, diagnosis, etiology and therapy.

2. A case of a forty-four year old white man with rheumatoid arthritis, keratoconjunctivitis sicca with lack of lacrimal secretions and bilateral, self-limited parotitis is presented.

3. The patient had, in addition, achalasia of the esophagus secondary to stricture at the esophagogastric junction.

4. Agglutination tests for rheumatoid arthritis (latex fixation, euglobulin agglutination and sheep cell agglutination) were positive. Biopsies

of the lacrimal and parotid glands failed to show lymphocytic infiltration.

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# Effects of Hypophysectomy and of Amphenone Administration in a Child with Functioning Metastatic Adrenal Carcinoma\*

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FUNCTIONING adrenal carcinomas, while rare, may present a formidable problem in management unless complete surgical removal can be accomplished [1–4]. Such tumors respond poorly to radiation [5,6] or chemotherapy [6].

Experimental work has shown that some endocrine tumors may develop or are maintained by hypersecretion of the pituitary trophic hormones [7]. In man, carcinomas of the thyroid appear to grow most rapidly when thyrothrophin production remains high [8]. On the other hand, most adrenal carcinomas have not seemed to be responsive to corticotrophin [9,10], although in some patients a rise in hormone output has been evoked by ACTH [10–12]. The few attempts to control adrenal tumors by hypophysectomy have been disappointing [13,14].

The possibility of control of the metabolic action of functioning tumors with pharmacologic agents has come under examination with the availability of amphenone, (3,3-di (p-aminophenyl) butanone-2-dihydrochloride), which blocks the production of corticosteroids in animals and man [15–19], and which leads to enlargement of the adrenal cortex and to lipid accumulation in the cells of the zonae fasciculata and reticularis in the presence of the intact pituitary [15,18]. Suppression of synthesis of both C-19 and C-21 compounds by addition of amphenone to perfused calf adrenals has also

been demonstrated [20]. Inhibition of corticosteroid production by amphenone has been clearly established in patients with adrenal carcinomas [6,19]. Toxic manifestations have included drowsiness, gastrointestinal symptoms and methemoglobinemia [18].

The possible benefit to be realized from hypophysectomy, chemotherapy and amphenone treatment was investigated in a girl whose adrenal tumor had recurred after surgical removal had been attempted.

#### MATERIAL AND METHODS

The patient was maintained on a controlled regimen in the metabolic ward of the Peter Bent Brigham Hospital. Determinations on urine, collected for successive twenty-four-hour periods, were carried out by the following methods: creatinine by a modification [21] of the Jaffé picric acid procedure [22]; glucose by the method of Froesch and Renold [23]; 17-hydroxycorticoids by the method of Reddy [24]; aldosterone by a modification [25] of the physicochemical method of Neher and Wettstein [26]; 17-ketosteroids by the alcoholic alkali colorimetric procedure after simultaneous acid hydrolysis and extraction of urine with toluene [27]; dehydroisoandrosterone-like compounds by Allen's adaptation [28] of the procedure described by Dirscherl [29], using the equation derived by Allen [30] to correct for interfering color in urine extracts; total ketonic steroids by a 2,4-dinitrophenylhydrazine procedure [31] which measures only 3- and 20-ketosteroids when the reaction mixture is cooled.

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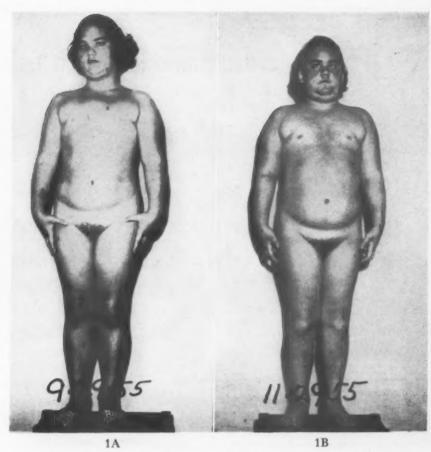


Fig. 1. Photographs of the patient. A, at seven years and seven months of age; B, at seven years and nine months of age. The increase in virilism (hirsutism of face, chest and legs; acne) and the accentuation of obesity and facial rounding in the two-month interval between photographs is evident.

By this differential reaction 17-ketosteroids are estimated indirectly; the unidentified group of ketonic steroids revealed by the discrepancy between this estimate and the 17-ketosteroids measured directly is called "X." All urinary steroids and glucose are expressed in terms of mg. per gm. of creatinine excreted. Since the patient's creatinine output ranged between 1.0 and 1.3 gm. per day most of the values given represent somewhat less than the twenty-four-hour excretion. Concentrations of free 17-hydroxy-corticoids in plasma were determined by the technic of Nelson and Samuels [32].

#### OBSERVATIONS

The patient was a girl under our observation from the age of seven years, seven months until her death at seven years, ten months. Details of the history and course are given in the appendix. Surgical excision of an adrenal tumor, followed by radiation of the tumor bed, was undertaken at the age of seven years and three months, three months after the first manifestations of virilism. Although the immediate

response was gratifying, symptoms recurred, a palpable mass developed in the left lower quadrant of the abdomen, and pulmonary metastases became evident at the age of seven years and six months.

At the age of seven years, seven months (Fig. 1A) the patient manifested virilization but had only slight manifestations of Cushing's syndrome. and moderate hypertension (130/100). During the period of observation there was marked aggravation of signs and symptoms of the endocrine disorder, including progressive virilization and hypertension (to 200/120) and development of obvious Cushing's syndrome with moonface, striae, voracious appetite, and glucosuria. (Fig. 1B.) Values for the rate of excretion of steroids paralleled the clinical picture and included: total ketonic steroids rising from 200 to 400 mg. per gm. of creatinine (normal 3 to 15 mg. per twenty-four hours); 17-ketosteroids rising from 70 to 203 mg. (normal 1 to 5); 17-hydroxycorticoids from 20 to 90 mg. (normal 1 to 10),

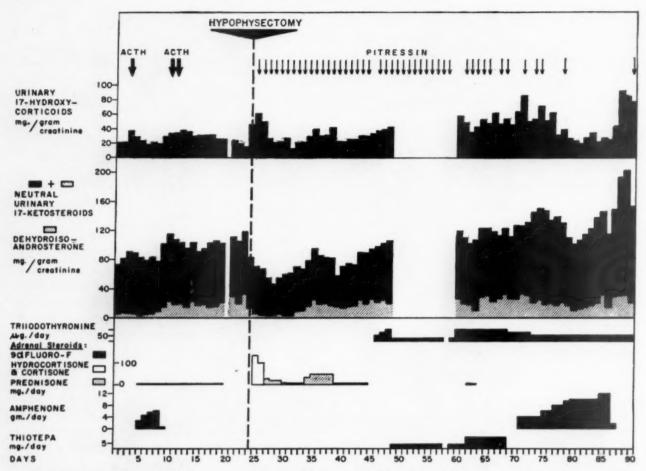


Fig. 2. Rate of excretion of 17-hydroxycorticoids and 17-ketosteroids. Major items of the therapeutic program are indicated. The interval between the forty-eighth and sixtieth day for which no urine samples are available represents the period during which the patient visited her home.

and aldosterone as high as 295  $\mu$ g. (normal 1 to 8  $\mu$ g.). The excretion of steroids observed during the patient's course is illustrated in Figures 2 and 3, as are the major items of the therapeutic program.

Three major efforts to influence the course of the disease were made.

Effects of Hypophysectomy. (a) Evidence for pituitary dependence: Corticotrophin, 80 units twice daily, was given intramuscularly on the third, eleventh and twelfth days. On each occasion there was a small increase in 17-hydroxy-corticoid excretion (Fig. 2), although a rise in 17-ketosteroids and total ketonic steroids occurred only on the first day of corticotrophin therapy. The concentration of 17-hydroxy-corticoids in the plasma increased from 21.4 to 36.1 µg. per 100 ml. on the first trial. These results were interpreted as suggesting that the tumor tissue might have some dependence on corticotrophin. There is considerable evidence that pituitary factors other than corticotrophin

and gonadotrophin (probably growth hormone) may favor the growth of tumors, since benefit may be achieved by hypophysectomy in patients previously adrenalectomized and gonadectomized in efforts to control cancer of the breast [33]. Although the experience of others with hypophysectomy for adult patients with functioning adrenal carcinomas has been disappointing [13,14] it was believed that in this young patient, who presumably was producing larger quantities of growth hormone than an adult, the possibility of benefit might be greater than in an adult.

(b) Observations Following Hypophysectomy: Hypophysectomy was performed on the twenty-fourth day by Dr. Donald Matson, using a transfrontal approach. The patient received 300 mg. of hydrocortisone intravenously the day of operation and thereafter decreasing amounts of cortisone acetate and then prednisone administered orally. The patient withstood the operation well and made a satisfactory recovery.

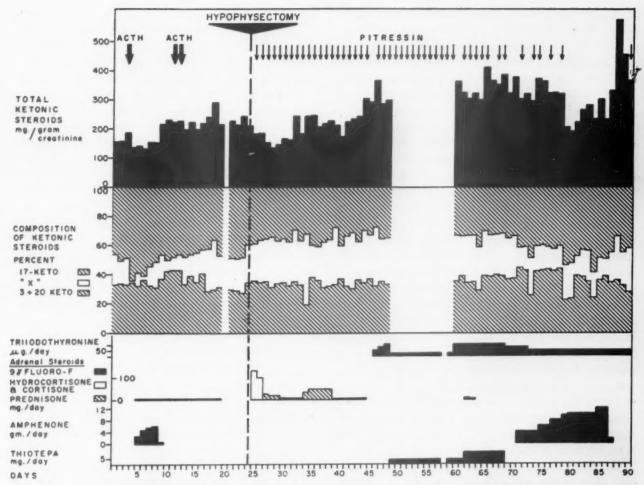


Fig. 3. Rate of excretion of total ketonic steroids and the proportion contributed by 17-ketosteroids, 3- and 20-keto-steroids and "X." The chart is otherwise identical with that shown in Figure 2.

Diabetes insipidus, which became evident on the day of operation, was readily controlled.

In the week following hypophysectomy there was a steady fall in the rate of excretion of 17ketosteroids to 47 mg., less than half the maximal preoperative value. The excretion of total ketonic steroids and dehydroisoandrosterone also fell. (Figs. 2 and 3.) Changes in corticosteroid excretion were more difficult to evaluate because of the exogenous steroids administered. During this period there was marked improvement in the patient's acne and the rate of growth of facial hair was obviously diminished. There appeared to be some improvement in the pulmonary lesions, as two small metastases became invisible in roentgenograms of the chest, although they reappeared three weeks later. Within a week, however, the rate of excretion of steroids rose again. Since the patient had been receiving large amounts of corticosteroids at the time improvement was observed, high doses of

prednisone were resumed for a few days. As the amount of 17-ketosteroid excreted continued to rise, it seemed clear that the dose of exogenous steroid was not a factor in endogenous production. There was no correlation between the rate of urine flow and rate of steroid excretion.

That hypopituitarism followed hypophysectomy was indicated by the persistence of diabetes insipidus and the development of hypothyroidism. Measurements of protein-bound iodine in the plasma or uptake of I<sup>131</sup> by the thyroid gland could not be relied upon as direct indices of thyroid function since an intravenous pyelogram had been performed immediately after admission. However, the serum cholesterol rose from 169 to 322 mg. per 100 ml. two weeks after operation, and the alkaline phosphatase activity of the plasma fell from 8.5 to 2.7 Bodansky units. At about the same time the patient complained of some distention and constipation, and perspired much less freely. She was given 100 μg.

of tri-iodothyronine daily, with considerable relief. With the exception of a brief period when she received only 25  $\mu$ g. daily, this dose was maintained until two weeks before her death. At that time the dose was reduced to 50  $\mu$ g. in an effort to counterbalance the hypermetabolism induced by the tumor.

Despite the clinical evidence of hypopituitarism, a small remnant of anterior pituitary cells was found beneath the dura of the sella turcica

at postmortem examination.

Effect of Thio-TEPA. Triethylene-thiophosphoramide (thio-TEPA), which has temporarily suppressed the growth of some solid tumors [34]. was given in two courses, first orally (3.5 mg. daily for ten days) and then intravenously (10 mg. daily for seven days) with no evidence of effect on the size or consistency of the abdominal tumor or any diminution in steroid excretion. During this treatment the pulmonary lesions increased in size. Although the number of white blood cells was unaltered, a drop in platelet count from 600,000 to 300,000 per cu. mm. suggested the possibility of impending bone marrow depression. Administration of the drug was discontinued since its toxic effect on the bone marrow may continue for some time after termination of therapy [34].

Effects of Amphenone Administration. Amphenone was administered orally on two occasions, before hypophysectomy for four days in amounts ranging from 3 to 6 gm. daily, and from the seventy-first day to the eighty-seventh day, in doses progressively increased from 4 to 12 gm. per day. The drug was given at two- or threehour intervals during the day and every four hours at night. During the first course the patient received 5 mg. of fluorohydrocortisone daily so that unpleasant symptoms resulting from any abrupt drop in hormone output would be minimized without serious interference with the evaluation of urinary steroid excretion [6]. At the time of the second course the manifestations of Cushing's syndrome were so severe that no fluorohydrocortisone was given. Instead, the dose of amphenone was increased very gradually. The only untoward symptom was transient dizziness for a brief period after each dose when the daily amount was 10 or 12 gm. No methemoglobinemia was detected by spectroscopic examination of the blood. The results of amphenone administration are shown in Figures 2 and 3.

Effect on 17-Hydroxycorticoid Excretion. In each instance there was a distinct reduction in 17-O H-

corticoid excretion. In the first course the output fell from 28.6 to 18.2 mg.; at the same time the plasma level fell from 27.3 to 9.6 µg. per 100 ml. The second course was begun when the corticosteroid excretion ranged between 45 and 64 mg. and glucose excretion was as high as 400 mg. per gm. of creatinine. On the tenth day of treatment corticoid excretion reached a low of 19.0 mg. and glucose was no longer measurable in the urine. Thereafter there was a gradual rise in corticoid excretion, although it remained lower than it had been before amphenone was given; there was no further glucosuria while the drug was administered. The plasma level of corticoids, which had been 54 µg. per 100 ml., was 33 mcg. on the ninth day of treatment and 36 mcg. on the sixteenth day. When amphenone therapy was discontinued there was an immediate increase of blood corticoids to 82 mcg. and the amount excreted was 91 mg., the highest observed in the patient's illness. On the succeeding two days the excretion was 85 and 76.6 mg. Glucosuria reappeared, 430 and 570 mg. being excreted on the two days after termination of amphenone.

Effect on 17-Ketosteroids and Androgens. The first trial of amphenone was believed not to have affected 17-ketosteroid excretion since the change was only from 88.4 to 78.8 mg. When amphenone was given from the second time the fall in 17-ketosteroid excretion was more impressive (from 126 to 100 mg.); at the same time there was an improvement in the patient's acne. Toward the end of this period there was some increase in 17-ketosteroids, but a much more pronounced rise when the drug was discontinued; 17-ketosteroid excretion then was as high as 193 and 203 mg.

Since the metabolites of amphenone which are excreted in the urine interfere to some degree with the determination of 17-ketosteroids-by increasing the color produced in the Zimmerman reaction-it is likely that the depression of 17-ketosteroid excretion during amphenone therapy was more pronounced than appears from Figure 2. This assumption is supported by the marked rebound increase in 17-ketosteroid excretion following withdrawal of amphenone and by changes which occurred in the urinary excretion of biologically measured androgen and of individual 17-ketosteroids as measured by paper chromatography. Individual 17-ketosteroids, particularly dehydroisoandrosterone and the 11-oxygenated 17-ketosteroids,

showed a dramatic decrease after initiation of amphenone therapy. Individual 17-ketosteroids were estimated by visual comparison of the unknowns with standards simultaneously carried through the chromatographic procedure and development of the chromatograms with the Zimmerman reaction; amphenone metabolites were removed and did not interfere with the reaction.

Dr. Paul L. Munson measured the biological activity of urine extracts by the chick-comb assay [35,36] and found that a control sample contained 355 \(\frac{1}{2}\) 1.33 International Units of androgen per twenty-four hours, a value greatly in excess of the normal range for adult men. During the first period of amphenone administration the androgen excretion of 201 \(\frac{1}{2}\) 1.14 I.U. per twenty-four hours was significantly lower (P < 0.001) than that of the control period. In the second course of amphenone treatment the value was 252 \(\frac{1}{2}\) 1.13 per twenty-four hours, which probably represented a real decrease since virilism had advanced greatly when this course of amphenone was instituted.

Effect on Total Ketonic Steroids. The excretion of these compounds was influenced in approximately the same way as the 17-ketosteroids, there being a fall of about one-third with amphenone and a rebound rise to very high levels at the end of the second course. The proportion of compounds each group contributed to the whole was also affected. In each course of amphenone the percentage of "X" declined abruptly when the drug was initiated, while the percentage of 17-ketosteroids increased. This pattern reverted to the pretreatment pattern when amphenone was stopped. The proportion of 3- and 20-ketosteroids did not change appreciably. (Fig. 3.)

Effect on Aldosterone. A few measurements of aldosterone excretion were made, late in the patient's hospitalization. The output was markedly above normal (295  $\mu$ g., normal 0 to 8) on the sixty-eighth day, but was only 36  $\mu$ g. after three days on amphenone.

Other Effects. As the second course of amphenone therapy continued it became evident that there was an improvement in the patient's clinical condition. Her blood pressure was occasionally as low as 140/100 mm. Hg, acne improved, the face was less rounded and less flushed. (Fig. 4.) At no time were there symptoms of hypoglycemia. The fasting blood sugar remained normal, and a 200 gm. carbohydrate

breakfast did not lead to an abnormal rise in blood sugar. Serum electrolytes remained normal and there was no dramatic change in electrolyte excretion. Diabetes insipidus was markedly ameliorated; no pitressin was required from the eighth day of amphenone until three days after the drug was discontinued.

Comments on the Use of Amphenone. Previous trials of amphenone in human subjects have indicated that its major effect on the adrenal is to decrease the release of carbohydrate-active corticosteroids [15,16,18,19] and of aldosterone [37]. The present observations show that biological androgens and 17-ketosteroids also are diminished. The changes noted do not reflect merely an influence on renal function, since the concentration of corticoids in blood was reduced and especially since there was a definite amelioration of Cushing's syndrome as evidenced by the improvement in the patient's appearance and the reduction of blood pressure. The decreased severity of diabetes insipidus was interpreted as reflecting the decreased production of those adrenal steroids (especially the corticoids) which usually aggravated diabetes insipidus by increasing the excretion of osmotically active substances [38].

Amphenone was withdrawn after sixteen days in order to evaluate whether the fall in steroid excretion represented blocking of output of hormone or a direct effect on the tumor. The moderate increase in steroid excretion during the last days of amphenone could have reflected escape from amphenone inhibition or continued growth of the tumor. The rebound elevation of steroids, to the highest levels observed in the patient's illness, suggested that the latter explanation is more likely, and that the drug had not served as a carcinolytic agent. Unfortunately, the patient died three days later. At postmortem examination there was extensive necrosis of the abdominal tumor and the metastases but this could not be differentiated clearly from that often observed in rapidly growing tumors.

It would have been of a great interest to observe the effect in this patient of DDD (2,2-bis [parachlorophenyl]-1,1-dichloroethane [39–41]) which is structurally quite similar to amphenone but which causes necrosis of the inner zone of the adrenal cortex of dogs, as well as a fall in corticosteroid production [42].

It is of interest to note a certain structural similarity (Fig. 5) between these two groups of compounds which have been shown to alter the



Fig. 4. Photographs of patient. A, before therapy at seven years and seven months of age; B, after hypophysectomy and four days before initiation of the second course of amphenone; C, on the last day of amphenone administration; D, three days later. Note the advance in evidence of virilism and Cushing's syndrome between A and B. The improvement in physical appearance consequent to amphenone therapy is evident in C. The aggravation of the disease after withdrawal of amphenone is reflected in the increased fullness of the patient's face and the fresh acne lesions shown in D.

3, 3 - di (p-aminophenyl) butanone - 2 dihydrochloride

(A)

2,2-di (p-chlorophenyl)-l.ldichloroethane

(B)

Fig. 5. The chemical structure of amphenone (A) and of DDD (B).

secretions of the adrenal cortex: (a) amphenone and its derivatives and (b) DDD and related compounds. While the changes induced in the adrenal cortex by amphenone are reversible, DDD produces necrosis of the inner zones of the adrenal cortex. Thus far, DDD has been shown to exert a clear-cut effect only in dogs. However, recent work of Nichols and Henniger [43] indicates that the species difference in response to DDD may be related to differences in the metabolism of the compound rather than to differences in susceptibility of the adrenal cortex itself.

#### SUMMARY AND CONCLUSIONS

Observations were made during a threemonth period (ages seven years and seven months to seven years and ten months) in a girl who died of a recurrent and metastasizing adrenal carcinoma which induced progressive virilism and Cushing's syndrome. Three approaches directed toward controlling the disease were made

Total hypophysectomy was performed, since some dependence of the tumor on corticotrophin was demonstrated and because of the possible stimulation of tumors by growth hormone. During the first week there was a fall in steroid excretion to less than one-half the preoperative levels and the acne improved markedly. Thereafter the disease advanced steadily. At postmortem examination a small but viable remnant of anterior pituitary cells was found. It is not clear whether the advance in tumor growth subsequent to apparent improvement should be ascribed to increased function of this remnant or to adaptation of the tumor to the new conditions. However, it is believed that the immediate

postoperative changes were sufficiently striking to suggest that hypophysectomy should again be seriously considered in future cases.

A course of oral and intravenous triethylenethiophosphoramide (thio-TEPA), a general carcinolytic agent, failed to influence the growth or function of the tumor.

Amphenone was administered orally for four days before hypophysectomy and for sixteen days beginning forty-seven days after the operation. This compound induced a distinct reduction in the excretion of all the steroids measured (corticosteroids, 17-ketosteroids, biological androgens, total ketonic steroids and aldosterone), complete disappearance of glucosuria, and improvement in the patient's physical appearance and hypertension. When amphenone was discontinued at the end of the second course the steroid excretion rose to the highest levels observed in the patient's illness, suggesting that the compound might have served to block hormone release rather than as a carcinolytic agent.

The failure of the therapeutic measures tried in this patient re-emphasize the fact that the best chance for survival in such patients still depends on complete removal of malignant tissue following prompt diagnosis. Physical changes induced by a functioning endocrine tumor should facilitate its early recognition.

#### APPENDIX

History, Findings and Hospital Course. S. L., a seven year and seven months old girl, was first admitted to the metabolic ward of the Peter Bent Brigham Hospital in September 1955. The past history was essentially uneventful with the exception of four brief episodes of headache

associated with vomiting at the age of four and one-half years. Hypertension was noted on one of these occasions but no other abnormality was found and these symptoms did not recur. Subsequent blood pressure readings were within normal limits. The child had always been tall and rather heavy, as were her parents and most of her relatives. Seven months before admission the growth rate accelerated, her voice deepened, acne developed and the appearance of pubic and facial hair was noted. The 17-ketosteroid excretion was 71.4 mg. per twenty-four hours, dehydroisoandrosterone 21.4 mg. and corticosteroid excretion was slightly elevated. In May 1955, four months before admission, a left adrenal cortical carcinoma was removed and cobalt radiation was directed to the tumor bed. Marked improvement in the physical signs resulted, and the 17-ketosteroid excretion fell to 3.6 mg. per twenty-four hours. However, late in August 1955, one month before admission, acne and hirsutism recurred, cough developed, 17ketosteroid excretion was 41.9 mg. per twentyfour hours, and two metastatic lesions were found in the upper lobe of the right lung. Cobalt radiation was administered to the lung lesion and the patient was referred to the Children's Cancer Research Foundation and admitted to the metabolic ward of the Peter Bent Brigham Hospital. The family history was non-contributory except, perhaps, that the paternal grandfather had diabetes mellitus. One brother, age five and one-half years, was in good health.

On admission the patient was 145.8 cm. tall and weighed 57.8 kg. Her height age was thus twelve years and her weight age more than sixteen years. Her musculature was unusually well developed. There was moderate generalized obesity with some rounding of the face. The skin was excessively moist, with considerable facial acne and seborrhea. The head was normal. There was marked myopia, with normal optic fundi. Dentition was normal for the child's age. Growth of axillary hair was beginning. The heart and lungs were normal. The blood pressure was 130/100 mm. Hg. There was no evidence of breast development. There was a very firm, fixed, non-tender mass, 10 by 15 cm. in the left lower quadrant of the abdomen. The adrenalectomy scar was well healed and not pigmented. Examination of the genitalia showed pubic hair, an enlarged clitoris and separate vaginal and urethral orifices. A vaginal smear showed immature cells.

Initial laboratory findings were: serum nonprotein nitrogen 31 mg. per 100 ml., fasting blood sugar (Folin-Wu) 107 mg. per 100 ml., total protein 6.5 gm. per 100 ml. (albumin 4.9, globulin 1.6), CO<sub>2</sub> combining power 25 mM. per L., chloride 102, sodium 137 and potassium 4.1 mEq. per L.; phosphorus 4.5, calcium 8.6 mg. per 100 ml., alkaline phosphatase activity 18 Bodansky units per 100 ml., cholesterol 150 mg. per 100 ml. The hemoglobin was 12 gm. per 100 ml., red blood cells 4.64 millions and white blood cells 10,400 per cu. mm., with a normal differential count. Glucose and insulin tolerance tests were within normal limits. Roentgen examination of the chest showed two rounded nodules in the upper lobe of the right lung; there were neither osseous metastases nor osteoporosis. The skeletal age was twelve years. An intravenous pyelogram demonstrated moderate downward displacement of the left kidney. Barium enema showed the colon to be displaced medially, without evidence of invasion of the colon by the tumor mass.

The urinary 17-ketosteroid excretion initially was 72 and 80 mg., dehydroisoandrosterone 4.5 and 7.6 mg., and 17-hydroxycorticoids 20.7 and 21.4 mg. per gm. of creatinine. The normal values for this age are less than 5 mg. for 17-ketosteroids, no dehydroisoandrosterone, 1 to 10 mg. for 17 hydroxycorticoids. The steroid excretions observed during the patient's course are illustrated in Figures 2 and 3 and have been discussed previously, as have been the indication for and the results of hypophysectomy, thio-TEPA and amphenone administration.

Despite the episodes of temporary improvement discussed previously, the endocrine disorder advanced markedly and relentlessly, with progressive virilism, hypertension (to 200/100 mm. Hg) and development of obvious Cushing's syndrome (Fig. 1B), evidenced by moonface, cervical fat pad, striae, voracious appetite and glucosuria. From September to December 1955 the patient's weight increased from 57.8 to 67.5 kg. with only 1.3 cm. gain in height. At no time was there clinical evidence of metastases to the liver or the skeletal system.

Twenty-three days posthypophysectomy the patient was permitted to leave the hospital for a week's stay at home. She was discharged taking 300 mg. of dilantin<sup>®</sup> daily, as well as pitressin<sup>®</sup> when required, and tri-iodothyronine. In addition, 3.5 mg. of triethylene-thiophosphoramide (thio-TEPA) was to be given orally daily. On

the fourth day at home the patient seemed febrile, and had a generalized tonic convulsion which was controlled with diffculty after one hour. She was admitted to a hospital in New York, where right upper lobe pneumonia was discovered and treated. After this acute episode the patient was readmitted to the metabolic ward of the Peter Bent Brigham Hospital. Roentgenologic examination indicated that the pulmonary lesions had grown and that new metastases had appeared in the left lung. An electroencephalogram demonstrated generalized abnormal slow activity although there were no neurological abnormalities. Dilantin administration was continued. Serum electrolytes continued to be normal. On the third day after the second and prolonged course of amphenone therapy the patient experienced a generalized convulsion. The airway was kept clear and considerable improvement had been effected with intramuscular barbiturate when the patient suddenly became cyanotic and died despite all efforts at resuscitation.

Postmortem Examination. The body weight was 67.5 kg., height 149 cm., an obese, moonfaced, hirsute young girl with prominent male escutcheon of pubic hair. Inspection revealed purple striae over the thighs, florid acne, well healed craniotomy and left adrenalectomy scars. There was no abnormal pigmentation. No breast development was apparent. The left perinephric fat, the hilus of the left kidney and the left iliac fossa contained many large, yellow, soft, partially necrotic tumor nodules. Tumor nodules were found in the tracheobronchial lymph nodes and in both lungs, mainly in the hilar regions; the largest nodules measured 3 to 4 cm. in diameter. Upon microscopic examination the tumor tissue was seen to consist of broad sheets of relatively undifferentiated, pleomorphic cells with eosinophilic, finely vacuolated cytoplasm; extensive areas of necrosis were seen in all sections. The right adrenal gland weighed 2 gm. and showed marked cortical atrophy on microscopic examination. The zona reticularis accounted for approximately one-half the width of the cortex, the zona glomerulosa and the zona fasciculata for approximately one-fourth each. Moderate vacuolation of all layers was observed but was most prominent in the fasciculata.

The pituitary fossa appeared grossly empty, but microscopic examination of sagittal sections through the fossa region revealed viable remnants of the pars anterior beneath the dura. The

predominent cells were of the finely granular eosinophilic and of the amphophilic series. The thyroid weighed 10 gm. and showed a diffuse increase in interstitial tissue but appeared otherwise normal. The ovaries weighed 3.5 gm. each; their histological appearance was consistent with the chronological age. Many ova were seen, as were numerous follicles and occasional corpora atretica. The uterus revealed a prepubescent endometrium on cross section. There was generalized visceromegaly with increased weight but normal appearance for all viscera (weight of heart 310 gm.; liver, 2,810 gm.; spleen 185 gm.; right kidney 155 gm.; left kidney 160 gm.). The brain appeared normal. There was partial atelectasis of the lungs with congestion and edema. No explanation for the terminal episode was found.

Acknowledgment: We are indebted to Dr. Roy Hertz for providing the amphenone administered to the patient.

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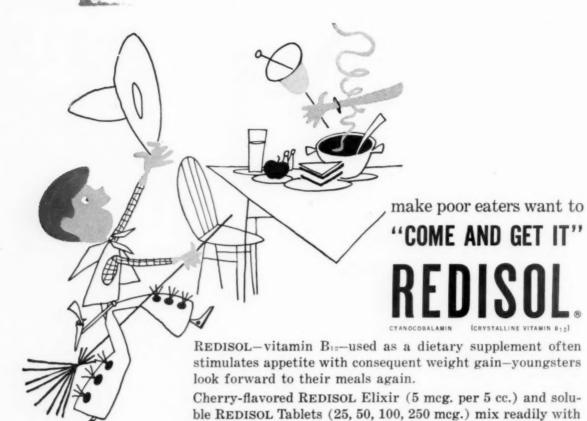
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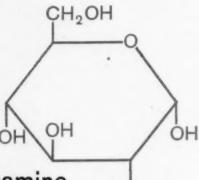


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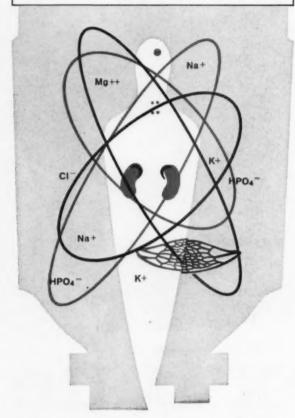
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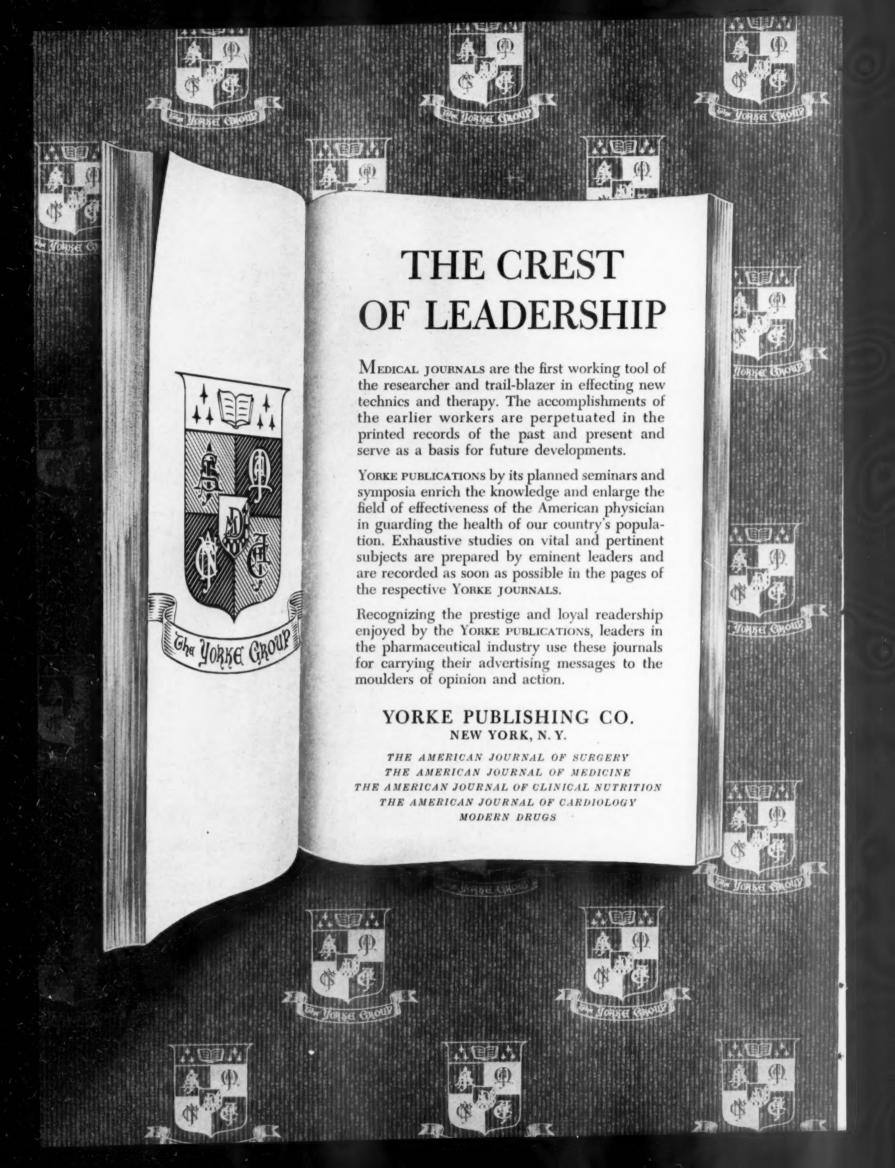
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CLINICAL RESULTS

DISEASE ENTITY

Acute back pain due to

- (a) Muscle spasm secondary to sprain
- (b) Muscle spasm due to
- (c) Muscle spasm due to nerve irritation
- (d) Muscle spasm secondary to discegenic disease and postoperative orthopedic procedures

Miscellaneous (bursitis, torticollis, etc.)

TOTAL

# bazzin

(Methocarbamol Robins, U.S. Pat. No. 2770649)

### Highly specific action

ROBAXIN is highly specific in its action on the internuncial neurons of the spinal cord — with inherently sustained repression of multisynaptic reflexes, but with no demonstrable effect on monosynaptic reflexes. It thus is useful in the control of skeletal muscle spasm, tremor and other manifestations of hyperactivity, as well as the pain incident to spasm, without impairing strength or normal neuromuscular function.

### Beneficial in 94.4% of cases tested

When tested in 72 patients with acute back pain involving muscle spasm, Robaxin induced marked relief in 59, moderate relief in 6, and slight relief in 3 – or an over-all beneficial effect in 94.4%. 1,3,4,6,7 No side effects occurred in 64 of the patients, and only slight side effects in 8. In studies of 129 patients, moderate or negligible side effects occurred in only 6.2%. 1,2,3,4,6,7

WITHE	ROBAXIN	IN ACUTE	BACK	PAIN 1, 3, 4, 6, 7

NO. OF CASES	DURATION OF TREATMENT	OF DOSE PER DAY (divided)		neg.	SIDE EFFECTS		
18	2-42 days	3-6 Gm.	17	1	0	0	None, 16 Dizziness, 1 Slight nausea,
13	1-42 days	2-6 Gm.	8	1	3	1	None, 12 Nervousness, 1
5	4-240 days	2.25-6 Gm.	4	1	0	0	None, 5
30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25 Dizziness, 1 Lightheaded- ness, 2 Nausea, 2 *
6	3-60 days	4-8 Gm.	6	a	0	0	None, 6
72			59	6	3	4	*Relieved on reduction of dose

References: 1. Carpenter, E. B.: Publication pending. 2. Carter, C. H.: Personal communication. 3. Forsyth, H. F.: Publication pending. 4. Freund, J.: Personal communication. 5. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: American Pharm. Assn. 46:374, 1957. 6. Nachman, H. M.: Personal communication. 7. O'Doherty, D.: Publication pending. 8. Truitt, E. B., Jr., and Little, J. M.: J. Pharm. & Exper. Therap. 119:161, 1957.

Indications — Acute back pain associated with: (a) muscle spasm secondary to sprain; (b) muscle spasm due to trauma; (c) muscle spasm due to nerve irritation; (d) muscle spasm secondary to discogenic disease and postoperative orthopedic procedures; and miscellaneous conditions, such as bursitis, fibrositis, torticollis, etc.

Dosage - Adults: Two tablets 4 times daily to 3 tablets every 4 hours. Total daily dosage: 4 to 9 Gm. in divided doses.

Precautions — There are no specific contraindications to Robaxin and untoward reactions are not to be anticipated. Minor side effects such as lightheadedness, dizziness, nausea may occur rarely in patients with unusual sensitivity to drugs, but disappear on reduction of dosage. When therapy is prolonged routine white blood cell counts should be made since some decrease was noted in 3 patients out of a group of 72 who had received the drug for periods of 30 days or longer.

Supply - Robaxin Tablets, 0.5 Gm., in bottles of 50.

A. H. ROBINS CO., INC., Richmond 20, Va. Ethical Pharmaceuticals of Merit since 1878

# **ESTABLISHED**

# OHLO BOM

### **COMBATS MOST CLINICALLY IMPORTANT PATHOGENS**

In a recent report of five years' experience involving 2,142 patients, the authors conclude that CHLOROMYCETIN (chloramphenicol, Parke-Davis) is a valuable and effective antibiotic in the treatment of various acute infectious diseases.<sup>1</sup>

Other current reports of *in vivo* and *in vitro* studies agree that CHLOROMYCETIN has maintained its effectiveness very well against both gram-negative<sup>2-6</sup> and gram-positive<sup>2,6-10</sup> organisms.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES (1) Woolington, S. S.; Adler, S. J., & Bower, A. G., in Welch, H., & Marti-Ibanez, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 365. (2) Ditmore, D. C., & Lind, H. E.: Am. J. Gastroenterol. 28:378, 1957. (3) Hasenclever, H. E.: J. Iowa M. Soc. 47:136, 1957. (4) Waisbren, B. A., & Strelitzer, C. L.: Arch. Int. Med. 99:744, 1957. (5) Holloway, W. J., & Scott, E. G.: Delaware M. J. 29:159, 1957. (6) Rhoads, P. S.: Postgrad. Med. 21:563, 1957. (7) Petersdorf, R. G.; Bennett, I. L., Jr., & Rose, M. C.: Bull. Johns Hopkins Hosp. 100:1, 1957. (8) Royer, A.: Changes in Resistance to Various Antibiotics of Staphylococci and Other Microbes, paper presented at Fifth Ann. Symp. on Antibiotics, Washington, D. C., Oct. 2-4, 1957. (9) Doniger, D. E., & Parenteau, Sr. C. M.: J. Maine M. A. 48:120, 1957. (10) Josephson, J. E., & Butler, R. W.: Canad. M. A. J. 77:567 (Sept. 15) 1957.

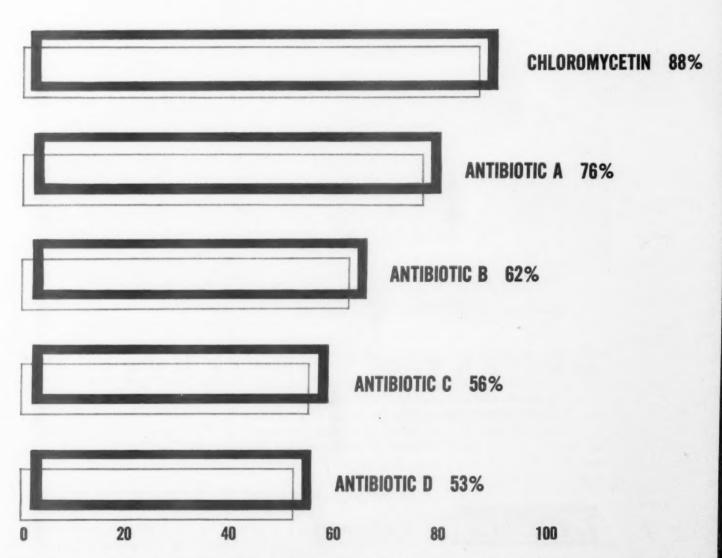
PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN



## **EFFICACY**

# MGET IN

IN VITRO SENSITIVITY OF MIXED PATHOGENS TO CHLOROMYCETIN AND 4 OTHER WIDELY USED ANTIBIOTICS\*



\*Adapted from Ditmore and Lind.\* Organisms tested were isolated from stools of 48 patients.



a study of 12,880 hypertensive patients

No. of Patients	Results	Percent
3,929	excellent	30.5%
6,393	good	49.6%
1,535	fair	11.9%
596	unsatisfactory	4.6%
427	side effects	3.3%

The tabulations at the left are from the recently completed study on cryptenamine (Unitensen) in which 12,880 patients and 1,384 physicians participated. Evaluation of the drug was based on experience in everyday private practice.

A summary of the "proof in practice" study is available upon request from the Medical Director of Irwin, Neisler & Co.

### UNITENSEN

UNITENSEN-R

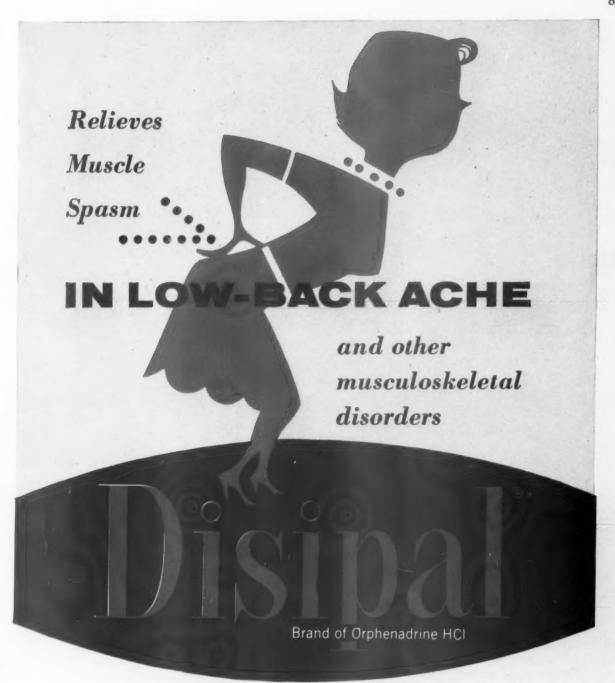
Each Unitensen tablet contains cryptenamine (tannates) 2.0 mg.

Each Unitensen-R tablet contains cryptenamine (tannates) 1.0 mg., Reserpine 0.1 mg.

Clinical supplies available upon request.



Irwin, Neisler & Co. . Decatur, Illinois



### In Parkinsonism

Highly selective action...energizing against weakness, fatigue, adynamia and akinesia...potent against sialorrhea, diaphoresis, oculogyria and blepharospasm... lessens rigidity and tremor... alleviates depression...safe... even in glaucoma.

\*Trademark of Brocades-Stheeman & Pharmacia, U.S. Patent No. 2,567,351. Other patents pending.

### Relieves Spasm, Pain, and Depression too

In muscle spasm due to sprains, strains, herniated intervertebral disc, fibrositis, noninflammatory arthritic states and many other musculoskeletal disorders, the first demand is for relief. Disipal fills this need. It is quickly effective in skeletal muscle spasm almost regardless of origin. Its mood-alleviating effect braces the patient against the depression so often accompanying severe pain of any type.

Dosage: 1 tablet (50 mg.) t.i.d.



LOS ANGELES



### for an active pregnancy

You make life easier for your pregnant and lactating patients when you prescribe new FILIBON—a welcome advance in prenatal supplementation. Important new features ensure increased comfort, convenience and efficiency . . . at no increase in cost.

MORE AGREEABLE... because of new, better tolerated ferrous fumarate... convenient one capsule per day administration.

**MORE EFFECTIVE** . . . because of new, non-inhibitory intrinsic factor assuring greater  $B_{12}$  absorption to meet increased needs . . . new, more comprehensive formulation with *phosphorus-free* calcium, Vitamins K and  $B_6$ , and important minerals and trace elements.

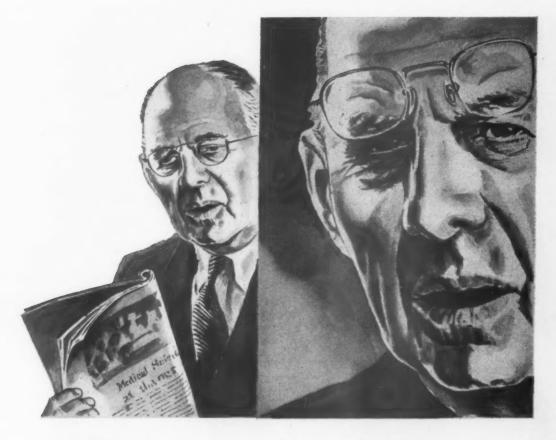
**MORE DEPENDABLE** . . . because new Reminder Jar stays on her dining table . . . ensures regular daily dosage, as prescribed.

### Each capsule contains:

Vitamin A	4,000 U.S. P. Units
Vitamin D	. 400 U. S. P. Units
Thiamine Mononitrate (B1).	3 mg.
Pyridoxine (B <sub>6</sub> )	1 mg.
Niacinamide	10 mg.
Riboflavin (B <sub>2</sub> )	2 mg.
Vitamin B <sub>12</sub>	2 mcgm.
Ascorbic Acid (C)	20 mg.
Vitamin K (Menadione)	0.5 mg.
Folic Acid	1 mg.
Ferrous Fumarate	
Iron (as Fumarate)	30 mg.
Intrinsic Factor	
Fluorine (as CaF <sub>2</sub> )	
Copper (as CuO)	
Iodine (as KI)	0.01 mg.
Potassium (as K2SO4)	0.835 mg.
Manganese (as MnO <sub>2</sub> )	
Magnesium (as MgO)	
Molybdenum (as Na <sub>2</sub> MoO <sub>4</sub> . 2	$(H_2O)$ 0.025 mg.
Zinc (as ZnO)	0.085 mg.
Calcium Carbonate	575 mg.
Dosage: one or more capsules of	faily.
Supplied: attractive, re-usable bo	ottles of 100 capsules.



LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK



### "Doctors can't help shingles?"

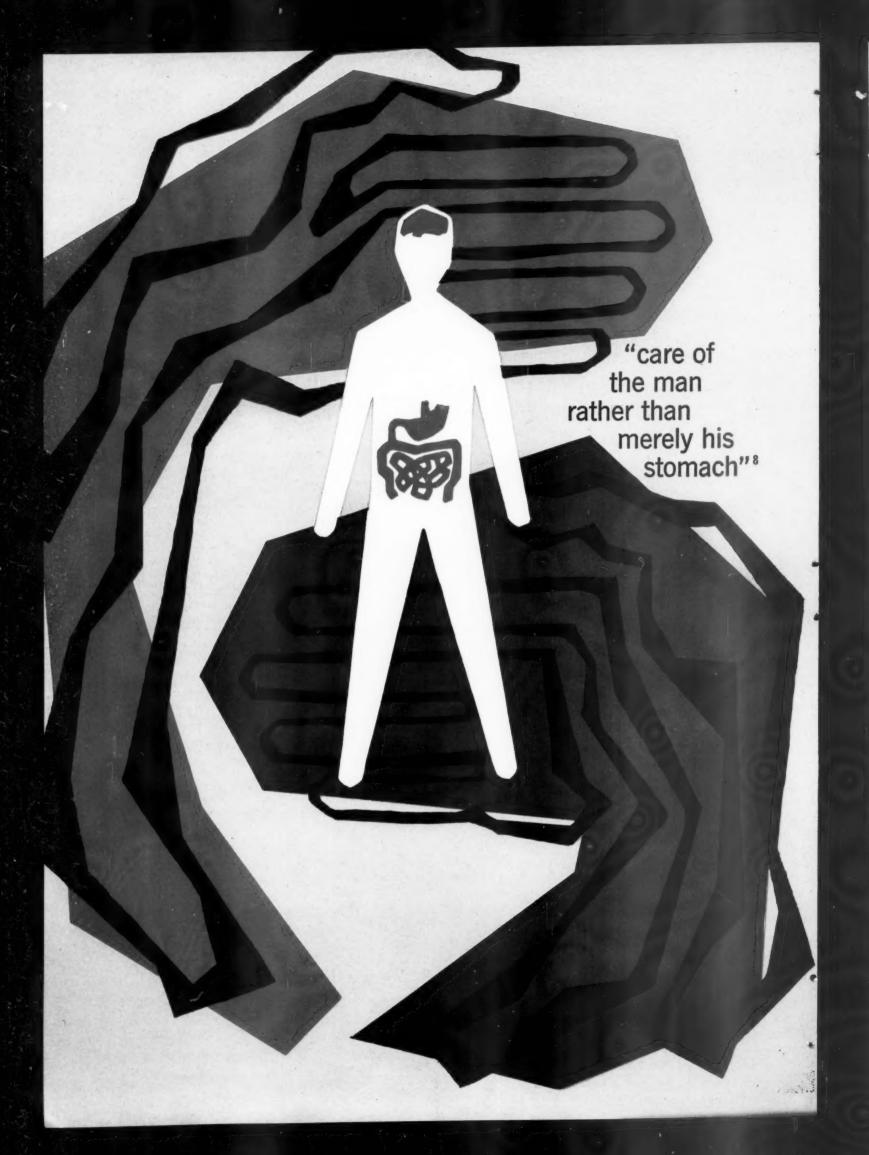
Physicians who have used Protamide extensively deplore such statements as unfortunate when they appear in the lay press. They have repeatedly observed in their practice quick relief of pain, even in severe cases, shortened duration of lesions, and greatly lowered incidence of postherpetic neuralgia when PROTAMIDE was started promptly. A folio of reprints is available. These papers report on zoster in the elderly the severely painful cases - patients with extensive lesions. Protamide users know "shingles" can be helped.

### PROTAMI

Sherman Laboratories

Detroit 11, Michigan

Available: Boxes of 10 ampuls - prescription pharmacies.





two-level control of gastrointestinal dysfunction

### at the central level

The tranquilizer Miltown® reduces anxiety and tension. 1,3,6,7 Unlike the barbiturates, it does not impair mental or physical efficiency.5,7

### at the peripheral level

The anticholinergic tridihexethyl iodide reduces hypermotility and hypersecretion.

Unlike the belladonna alkaloids, it rarely produces dry mouth or blurred vision.<sup>2,4</sup>

indications: peptic ulcer, spastic and irritable colon, esophageal spasm, G. I. symptoms of anxiety states.

### each "Milpath" tablet contains:

Miltown® (meprobamate WALLACE) (2-methyl-2-n-propyl-1,3-propanediol dicarbamate) 

dosage: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

available: bottles of 50 scored tablets.

#### references:

references:

1. Atschul, A. and Billow, B.: The clinical use of meprobamate (Mittown®).

New York J. Med. 57:2361, July 15, 1957. 2. Atwater, J. S.: The use of anticholinergic agents in peptic ulcer therapy. J. M. A. Georgia 45:421, Oct. 1956. 3. Borrus, J. C.:

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Experimental studies of behavioral effects of meprobamate on normal subjects. Ann. New York Acad. Sc. 67:701, May 9, 1957. 6. Phillips, R. E.: Use of meprobamate (Miltown®) for the treatment of emotional disorders. Am. Pract. & Digest Treat. 7:1573, Oct. 1956. 7. Selling, L. S.: A clinical study of Miltown®, a new tranquilizing agent. J. Clin. & Exper. Psychopath. 17:7, March 1956. 8. Wolf, S. and Wolff, H. G.: Human Gastric Function, Oxford University Press, New York, 1947.



WALLACE LABORATORIES

New Brunswick, N. J.

# CHLOROTHIAZIDE)

in

## **EDEMA**

Start therapy with one or two 500 mg. tablets of 'DIURIL' once or twice a day.

### BENEFITS:

- The only orally effective nonmercurial agent with diuretic activity equivalent to that of the parenteral mercurials.
- Excellent for initiating diuresis and maintaining the edema-free state for prolonged periods.
- Promotes balanced excretion of sodium and chloride—without acidosis.

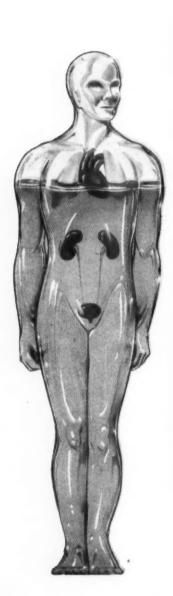
Any indication for diuresis is an indication for 'DIURIL':

Congestive heart failure of all degrees of severity; premenstrual syndrome (edema); edema and toxemia of pregnancy; renal edema—nephrosis; nephritis; cirrhosis with ascites; drug-induced edema. May be of value to relieve fluid retention complicating obesity.

SUPPLIED: 250 mg. and 500 mg. scored tablets 'DIURIL' (chlorothiazide); bottles of 100 and 1,000.
'DIURIL' and 'INVERSINE' are trade-marks of Merck & Co., Inc.



MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa.



as simple as 1-2-3 in

HYPERTENSION

INITIATE 'DIURIL' THERAPY
'DIURIL' is given in a dosage range of from 250

'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day.

ADJUST DOSAGE OF OTHER AGENTS

If the patient is established on a ganglionic blocking agent (e.g., 'INVERSINE') this should be continued, but the total daily dose should be *immediately* reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade. The dosage of other antihypertensive medication is adjusted as indicated by patient response.

ADJUST DOSAGE OF ALL MEDICATION

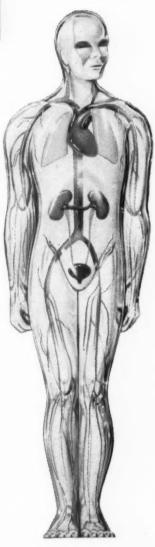
The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

### BENEFITS:

- improves and simplifies the management of hypertension
- · markedly enhances the effects of antihypertensive agents
- reduces dosage requirements for other antihypertensive agents—often below the level of distressing side effects
- smooths out blood pressure fluctuations

INDICATIONS: management of hypertension

Smooth, more trouble-free management of hypertension with 'DIURIL'



# when you encounter gastrointestinal genitourinary infections

for all tetracycline-amenable infections, prescribe superior

SUM



# respiratory infections infections



miscellaneous

infections



In your patients, SUMYCIN produces: 1. Superior initial tetracycline blood levels-faster and higher than ever before - assuring fast transport of adequate tetracycline to the site of the infection. 2. High degree of freedom from annoying or therapy-interrupting side effects.

> Tetracycline phosphate complex equiv. to tetracycline HCI (mg.)

Packaging:

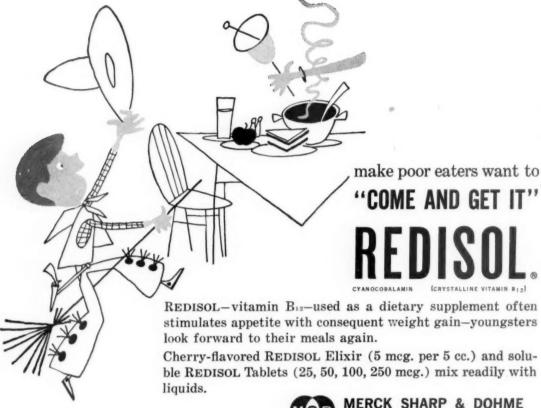
Sumycin Capsules (per Capsule)	250	Bottles of 16 and 100
Sumycin Suspension (per 5 cc.)	125	2 oz. bottles
Sumycin Pediatric Drops (per cc.—20 drops)	100	10 cc. dropper bottles
Sumycin Intramuscular with Xylocaine*	100	1 dose vials



Supply:



Squibb Quality—the Priceless Ingredient

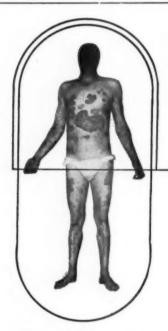


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## **PSORIASIS**

Proved Clinically Effective Oral Therapy maintenance regimen may keep patients lesion-free.

> COMPLETE LITERATURE AND REPRINTS UPON REQUEST. JUST SEND AN Rx BLANK.

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Spirt & Co., Inc.

LIPAN Capsules contain: Specially prepared highly activated, desiccated and defatted whole Pancreas: Thiamin HCl, 1.5 mg. Vitamin D, 500 I.U.

Available: Bottles 180's, 500's.

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### **NOW**

## COUNTERACT DEPRESSED MOODS without stimulation

- Relieves depression without euphoria -not a stimulant
- Restores natural sleep without depressive aftereffects -not a hypnotic
- Rapid onset of action
- Side effects are minimal and easily controlled

Composition: Each tablet contains 400 mg. meprobamate and 1 mg. benactyzine HCl

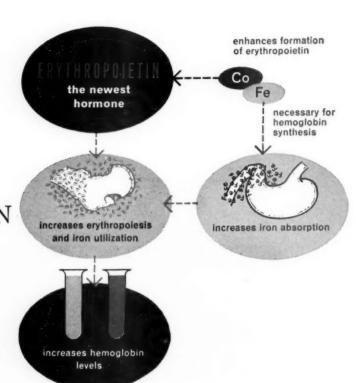
Average Adult Dose: 1 tablet q.i.d.

'Deprol'



WALLACE LABORATORIES, New Brunswick, N. J. Literature and samples on request

NEW
RESEARCH ON
ERYTHROPOIETIN
EXPLAINS
CLINICAL
SUPERIORITY OF



# RONCOVITE-mf

IN THE COMMON ANEMIAS

Elucidation of the action of erythropoietin—the erythropoietic hormone—provides a clear explanation for the observations of Holly, Ausman, Tevetoglu and many others who have reported that in the common anemias cobalt-iron therapy results in a clinical response superior to that produced by iron alone.

Increased Iron Absorption and Utilization—Recent investigations show that cobalt enhances the formation of erythropoietin. <sup>4,5</sup> This hormone increases the rate of production of new red cells which, in turn, increases the rate of both iron utilization by the marrow and iron absorption from the intestine. <sup>6</sup>

Clinical Application—In simple iron deficiency anemia, 89% of patients treated with Roncovite exceeded 12 Gm. of hemoglobin per 100 cc., while only 33% of the same patients treated with iron alone for a comparable period reached this level.<sup>2</sup> In anemia of pregnancy, 98.2% of Roncovite-

treated patients maintained their hematologic status; 63.8% delivered with a hemoglobin of 13 Gm. per 100 cc. or more. In anemia of infancy and childhood an average hemoglobin level of only 8.7 Gm. per 100 cc. was attained with iron alone while the same patients subsequently reached an average hemoglobin level of 11.6 Gm. per 100 cc. with Roncovite. 3

**Roncovite-MF** is the new therapeutic agent based on erythropoietin formation which translates this new research into the practical utility of full iron effectiveness with greatly decreased, better tolerated iron dosage.

Each enteric-coated, green tablet contains:

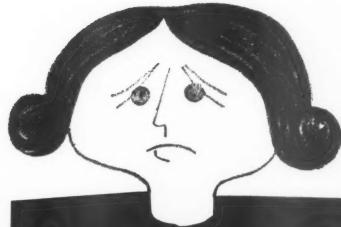
Cobalt chloride, 15 mg. Ferrous sulfate exsiccated, 100 mg.

Maximum adult dosage:

one tablet after each meal and at bedtime. Supplied: Bottles of 100 tablets.

Bibliography available on request.

LLOYD BROTHERS, INC.



when there's trouble, trouble everywhere... along her G.I. tract

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(DACTIL + PIPTAL in one tablet)

rapidly and dramatically effective1

cholinolytic of choice in a variety of gastrointestinal conditions1...relieves pain and spasm, normalizes motility and secretion1..."remarkably free of undesirable effects...."2

(1) Settel, E.: J. Am. Geriatrics Soc., January 1958. (2) Necheles, H., and Kirshen, M. M.: The Physiologic Basis of Gastrointestinal Therapy. New York, Grune & Stratton, Inc., 1957, p. 87.

Each TRIDAL tablet contains 50 mg, of the visceral eutonic DACTIL® (the only brand of piperidolate hydrochloride) and 5 mg. of the anticholinergic PIPTAL\* (the only brand of pipenzolate methylbromide). Bottles of 50 compressed, white tablets.

trouble



### Avoids Mental Cloudiness in hypertension therapy

Rautensin (the alseroxylon fraction of Rauwolfia) offers simple, safe, effective and easy-to-manage therapy for the complex problem of hypertension. Rautensin produces a gradual and sustained drop in blood pressure ... calms and soothes the anxious patient without loss of alertness...slows accelerated pulse. Patients on this regimen show marked reduction of anxiety with a simultaneous increase in intellectual and psychomotor efficiency.1

With the use of the alseroxylon fraction of Rauwolfia, side actions "...are either completely absent or so mild as to be inconsequential" and there is "...no danger of sudden rebound of the blood pressure."2 Furthermore, alseroxylon was found less prone to cause mental depression,8 and does not usually cause drowsiness. Rautensin is purified and therefore free of inert dross present in the whole root.

- Wright, W. T., Jr.; Pokorny, C., and Foster, T. L.: J. Kansas M. Soc. 57:410, 1956.
   Terman, L. A.: Illinois M.J. 3:67, 1957.
   Moyer, J. H.; Dennis, E., and Ford, R.: Arch. Int. Med. 96:530, 1955.

### Rautensin<sup>®</sup>

The purified alkaloid complex of Rauwolfia with total therapeutic activity-minimal side effects. Each tablet contains 2 mg. purified Rauwolfla serpentina alkaloids (alseroxylon fraction)

SMITH-DORSEY . Lincoln, Nebraska . A Division of The Wander Company

For better
tetracycline absorption,
higher serum levels
and more certain
control of infection...

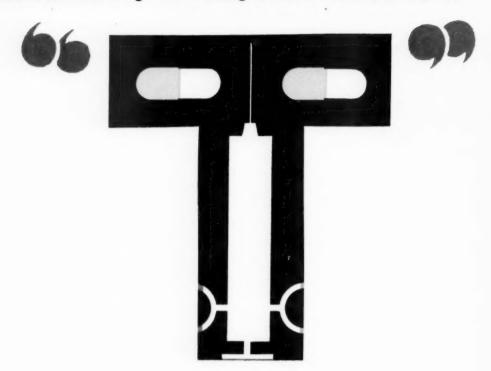


# Tetrex

In view of its higher blood levels..."it appears that tetracycline phosphate complex would be more effective [than tetracycline HCI] in treat-

ing infections due to susceptible organisms."4

Suits every tetracycline need to a



### Typical comments from clinical investigators

"The advantages of higher blood and tissue levels of tetracycline in combating infections with susceptible bacteria are significant." 1

"All patients with infections caused by tetracycline-sensitive organisms responded satisfactorily to tetracycline phosphate complex therapy."<sup>5</sup>

"The increased serum levels obtained with it [tetracycline phosphate complex] may be considered a 'safety factor'."

"It effectively controlled the pyogenic component . . ."9

"Side effects were infrequent and mild . . . "8

# Tetrex

THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX





Faster, higher tetracycline serum levels for more certain control of infection. 1,4,5,7,10,11

Significant serum levels for 24 hours on a single dose of Tetrex Intramuscular (250 mg.)<sup>2,3</sup>

A single, pure antibiotic (not a mixture.)

B.i.d. or q.i.d. dosage equally effective orally. 1, 6, 8, 11

Clinically "sodium-free."1,6

A dosage form for every tetracycline need.

References: 1, Cronk, G. A., Naumann, D. E., and Casson, K.: Fifth Annual Symposium on Antibiotics, Washington, D. C., Oct. 2-4, 1957.

2. Dube, A. H.: Ibid. 3, Portney, B., Draper, T., and Wehrle, P. F.: Ibid. 4, Shidlovsky, B. A., Prigot, A., Maynard, A. de L., Felix, A. J., and Hjelt-Harvey, I.: Ibid. 5, Cronk, G. A., and Naumann, D. E.: Ant. Med. & Clin. Ther. 4:166, 1957. 6, Prigot, A., Shidlovsky, B. A., and Felix, A. J.: Ibid. 4:487, 1957. 7, Pulaski, E. J., and Isokane, R. K.: Ibid. 4:408, 1957. 8, Putnam, L. E.: Ibid. 4:470. 1957. 9, Rein, C. R., and Fleischmajer, R.: Ibid. 4:422, 1957. 10, Welch, H., Lewis, C. N., Staffa, A. W., and Wright, W. W.: Ibid. 4:215, 1957. 11, Pulaski, E. J.: Practitioner 179:465, 1957.

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2 capsules (500 mg.)
b.i.d. provide
safe, effective,
time-saving therapy
for adults

A single (250-mg.) I.M.
adult dose produces
significant
24-hour serum
levels

Five groups of investigators who administered Tetrex to 996 patients with a wide variety of infections reported excellent therapeutic results, with a remarkably low incidence of side effects. <sup>1,5,6,8,9</sup> As one group reported: "All patients infected with tetracycline-sensitive organisms responded satisfactorily to therapy." In only 8 patients (0.8%) of the 996 were side effects such as to require discontinuance of therapy.

COMPLEX

As the need arises — a suitable dosage form: Tetrex Capsules (250 mg.), Tetrex Pediatric Capsules (100 mg.), Tetrex Intramuscular (250 mg.) with Xylocaine\*, Tetrex Intramuscular (100 mg.) with Xylocaine\*, Tetrex-APC with Bristamin.

Also Available: Tetrex Syrup and Tetrex Pediatric Drops (tetracycline syrup, phosphate buffered.)

\*® of Astra Pharm. Prod. Inc. for lidocaine.

Bristol LABORATORIES INC., Syracuse, N. Y.

### EFFECTIVE

in a wide
variety of
common
including:

### Respiratory tract intections:

pneumonia, acute bronchitis, pharyngitis, sinusitis, septic sore throat, whooping cough.

### Urinary tract

pyelonephritis, pyelitis, cystitis, prostatitis, urethritis.

### Gastrointestinal infections:

bacillary and amebic dysentery, bacterial diarrhea, gastroenteritis.

### Dermatologic

cellulitis, furunculosis, pustular dermatoses, acne.

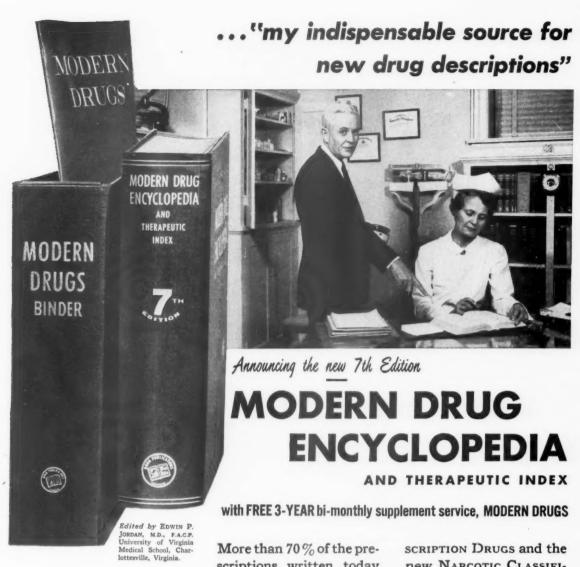
### Rickettsial and

typhus fever,
Rocky Mountain
spotted fever,
trachoma,
lymphogranuloma
venereum,
psittacosis.

### Prophylaxis in surgery and obstetrics:

preoperative preparation of gastrointestinal tract; deliveries in unsterile fields.



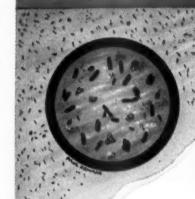


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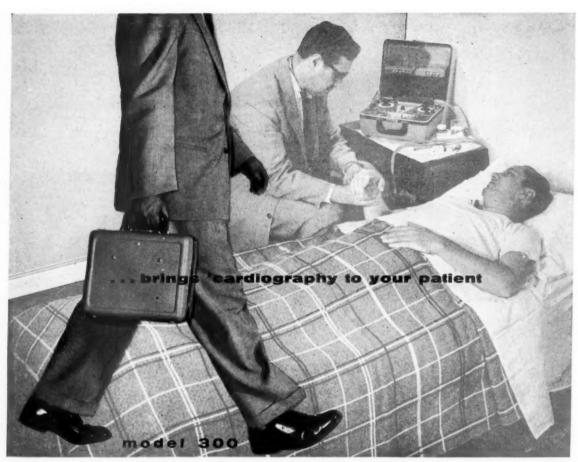
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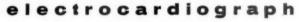


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References: (1) Russek, H. I.; Zohman, B. L.; Drumm, A. E.; Weingarten, W., and Dorset, V. J.: Circulation 12:169, 1955. (2) Dripps, R. D.: J.A.M.A. 139:148 (Jan. 15) 1949. (3) Dietz, G. W.: Am. Pract. & Digest Treat. 6:1872, 1955. (4) Lewis, B. I.; Lubin, R. I.; January, L. E., and Wild, J. B.: Circulation 14:227, 1956.

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Three steps are necessary-



in establishing correct eating patterns

supervision by the physician<sup>1,2,3</sup> a balanced eating plan<sup>1,2,3</sup> selective medication<sup>1,2,3</sup>

### Obedrin

and the 60-10-70 Basic Plan

Following the establishment of desired eating patterns—the maintenance of the acquired habits is most important. Here, Obedrin and the 60-10-70 Plan can be valuable aids to both the physician and patient.

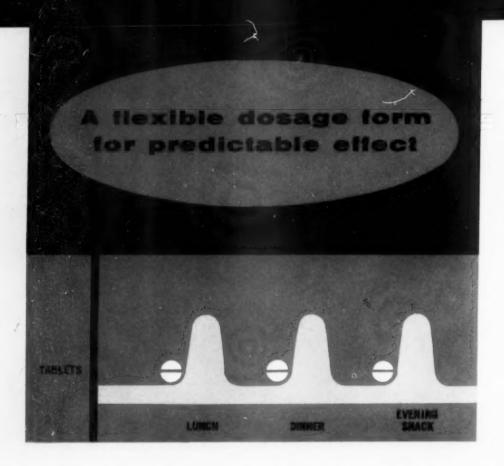
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- Methamphetamine for its proven anorexigenic and moodlifting effects.
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- · Ascorbic acid to aid in the mobilization of tissue fluids.

### Formula:

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Pentobarbital													-
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- 1. Eisfelder, H.W.: Am Pract. & Dig. Treat. 5 (Oct. 1954)
- 2. Freed, S.C.: G.P. 7:68 (1953)
- 3. Sherman, R.J.: Medical Times, 82:107 (Feb. 1954)



Obedrin tablets provide a flexible dosage form which may be prescribed to depress the appetite at peak hunger periods.

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A flexible dosage form

Minimal central nervous stimulation

Vitamins to supplement the diet

No hazards of impaction

and the 60-10-70 Basic Plan



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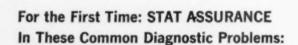
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2. Crush tablet.



4. Add 1 drop of color developer: mix.



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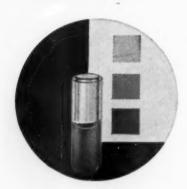
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Clinical control	tranquilization potentiates cor- ticoid effect for greater response	tranquilization eliminates or minimizes anxiety-induced exacer- bation, aggravation or relapse for superior control	dependable tranquilization achieves more consistent enhancing effectproved by marked success in 97 per cent of 735 cases*				
Dosage levels	corticoid requirements are often markedly reduced	tranquilizer enhancing effect frequently permits lower corticoid dosage	tranquilizer dosage levels are the lowestmore dependable tranquilization often allows lower corticoid dosage				
Toleration	corticoid side effects are sig- nificantly reduced or eliminated	no antihistamine sedation or other side effectsfewer corticoid side reactions	tranquilizer control is the safest  no report of blood dyscrasia or bone marrow aplasia in 735 cases  free of mental "fogging"  more consistent reduction of corticoid complications				
Patient management	tranquilization promotes active cooperation	tranquilization promotes active cooperation	reliable, uncomplicated tranquil- ization means better cooperation				

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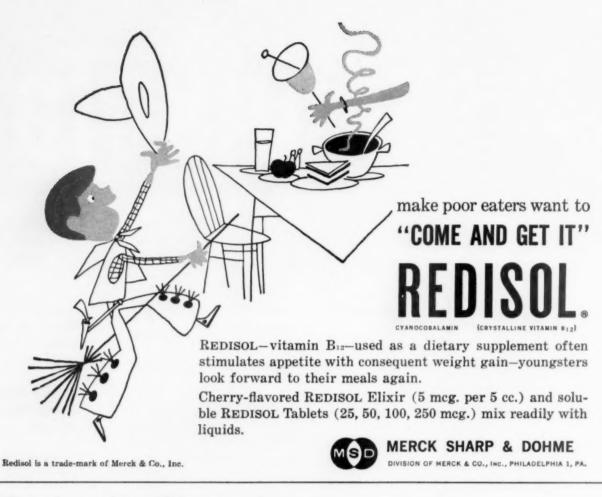
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management of the anginal par DOSAGE: One to two tablets q.i.d.

before meals and on retiring.



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- Reduces blood pressure in hypertensives, not in normotensives
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LOS ANGELES

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"It happened at work while he was putting oil in something"



"He told Mom his shoulder felt like it was on fire"



"He couldn't swing a bat without hurting"



"But Doctor gave him some nice pills -- and the pain went away fast"



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### AND THE PAIN WENT AWAY FAST

# **FOR PAIN**

ACTS FASTER... usually within 5-15 minutes

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### VERSATILE

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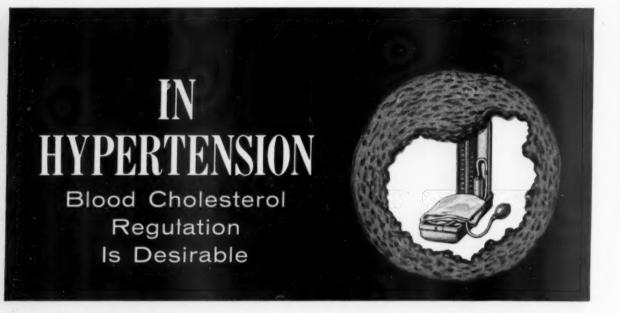
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Patients with hypertension develop atherosclerosis more rapidly and at a younger age than people with normal blood pressure. It is also known that clinical hypercholesteremia is associated with increased atherosclerosis and that many hypertensives show elevated cholesterol levels. For example, in one study including 120 patients with high blood pressure, hypercholesteremia was found in 44% of the hypertensive group.

The consensus of opinion today is that elevated cholesterol levels should be reduced or prevented, and it has been amply demonstrated that this can be done very well by adding linoleic acid and vitamin B<sub>6</sub> to the diet. In scores of patients with hypercholesteremia, and particularly in patients with vascular disease, diets high in linoleic acid produced improvement. <sup>4,5</sup> Vitamin B<sub>6</sub> is apparently necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Thus the body is dependent on an intake of both linoleic acid and vitamin B<sub>6</sub> for normal cholesterol levels. <sup>6,7</sup>

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Effects of anticholinergic drugs on peptic ulcer1

	Atropine	Anticholinergic A	Anticholinergic B	PATHILON
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length of follow-up	11 mo.	13 mo.	9 mo.	11 mo.
Results:				
Good to excellent	51%	74%	56%	76%
Fair to poor	49%	26%	44%	24%
Recurrences:				
None	16%	22%	13%	19%
Few	46%	48%	50%	57%
Same	38%	38%	38%	24%
Complications:				
Hemorrhage	5%	7%	19%	9.5%
Perforation	0%	4%	0%	0%
Obstruction	0%	4%	0%	0%
Surgery needed	3%	4%	6%	0%
Side effects:				
Oral	38%	78%	25%	14%
Visual	11%	48%	6%	0%
Sphincter	11%	15%	0%	0%

Available in three forms: tablets of 25 mg., plain (Pink) or with phenobarbital, 15 mg. (Blue), and parenteral, 10 mg./cc.-1 cc. ampuls.

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Parenterally, 10 to 20 mg. every 6 hours.

Also available: PATHIBAMATE\*\* Meprobamate with PATHILON LEDERLE, for gastrointestinal disorders and their "emotional overlay."

1. After Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer, Am. J. Digest. Dis. 1:301 (July) 1956.

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in anticholinergic therapy... weigh the benefits. against the side effects



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Simple to prescribe as merely PMB

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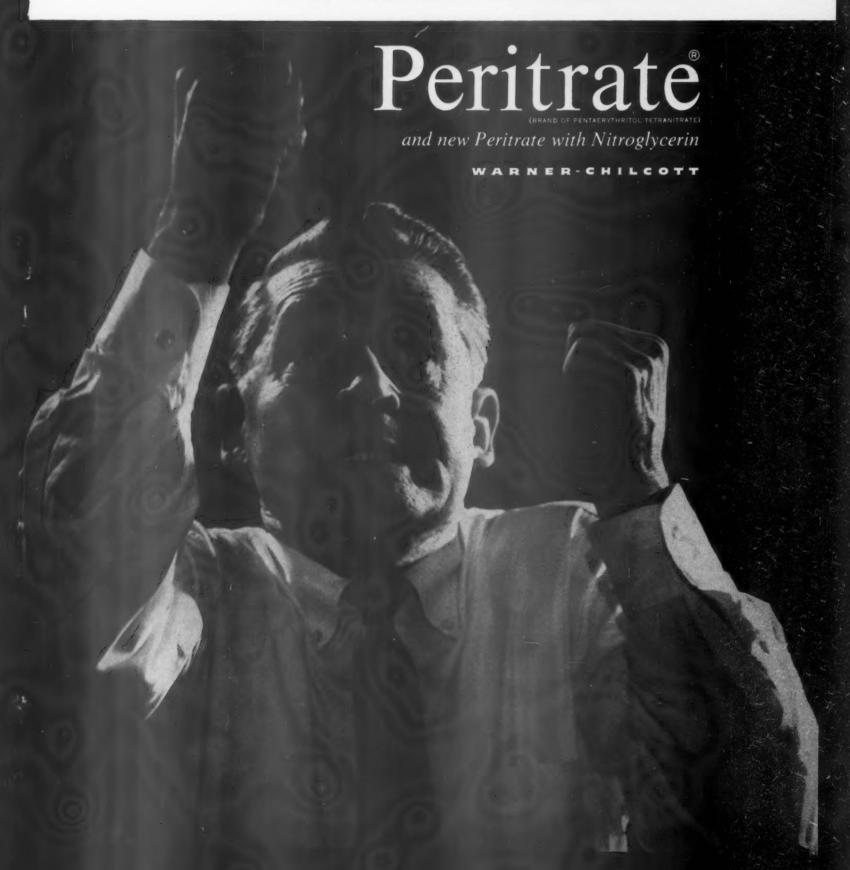
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the only available preparation chemically identical with naturally-occurring vitamin  $K_1$ ... "has a more prompt, more potent and more prolonged effect than the vitamin K analogues"

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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.

2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505,

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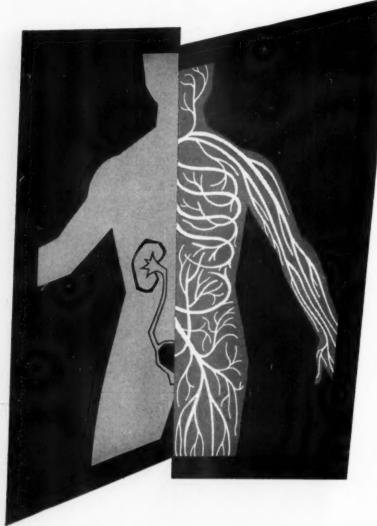
"it has fulfilled better than any previously tried medicaments all the qualifications" expected of a proctologic ointment

"promotes smooth epithelization and healthy granulation tissue and accelerates healing."

DESITIN CHEMICAL COMPANY, PROVIDENCE 4, R. I.

New RECTAL DESITIN OINTMENT is not to be confused with regular DESITIN OINTMENT

1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.



- Angiography
- Intravenous and retrograde urography

Versatile radiological agents with an unexcelled degree of safety

### RENOGRAFIN

Squibb Contrast Media

- well tolerated systemically and locally
- consistently good visualization
- convenient concentrations, in easily administered form

### **RENOGRAFIN 76%**

for intravenous urography and angiography. Ampuls of 20 cc., with 1 cc. ampul for sensitivity testing. Each cc. contains 760 mg. of sodium and methylglucamine diatrizoate.

### **RENOGRAFIN 60%**

for intravenous urography and angiography. Ampuls of 25 cc., with 1 cc. ampul for sensitivity testing. Each cc. contains 600 mg. of sodium and methylglucamine diatrizoate.

### **RENOGRAFIN 30%**

for retrograde pyelography. Rubber-capped vials of 50 cc. Each cc. contains 299 mg. of sodium and methylglucamine diatrizoate.

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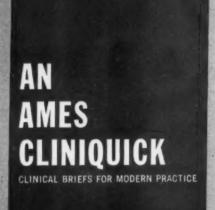


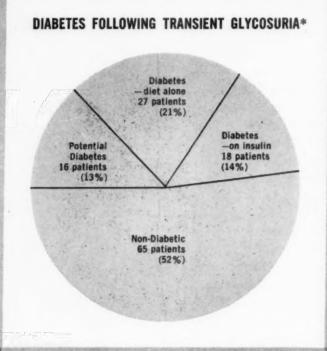
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### Advertisers Index

### March, 1958

Abbott Laboratories							*							Insert	Facin	g Page 5
Ames Company, Inc								×								. 4, 118
The Armour Laboratories									*							. 108
Ayerst Laboratories						*						17,	32,	Insert	Facing	Page 110
Bristol Laboratories, Inc.								36-	-37,	48-	49,	Inse	erts.	Facing	Pages	48 and 94
Burroughs Wellcome & Co., In																
Ciba Pharmaceutical Products,																
Cyclotherapy, Inc																
Desitin Chemical Company .																
Eaton Laboratories																
Endo Laboratories																. 107
Geigy Company																. 73
Harvard Medical School																
Hoffmann-La Roche, Inc																
Irwin, Neisler & Co																
Knoll Pharmaceutical Company																. 66
Lakeside Laboratories, Inc																
Lederle Laboratories Division,																
								21	20	43	-44	1-4	5 4	7 62-	63 75	, 82, 109
Eli Lilly and Company									,	,						. 64
Lloyd Brothers, Inc																92
The S. E. Massengill Company											Insi	erts	Fac	ing Pa	ges 16	and 102
McNeil Laboratories, Inc.																
Mead Johnson																
Merck Sharp & Dohme			*	1	2 1	7 2	8	30	40-	41	42	66.	86-	-87. 90	) 96	106, 113
Nordmark Pharmaceutical Labo																
Nuclear-Chicago Corporation .																
Organon Inc.																
Parke, Davis & Company																
Pfizer Laboratories, Division of	Char	. De	zer	R- 1	Co	In				*					38 68	-69 105
The Quaker Oats Company																
Riker Laboratories Inq																
A. H. Robins Co., Inc																
Roche Laboratories, Div. of Hoff																
William H. Rorer, Inc																
Sanborn Company																
Schering Corporation																
G. D. Searle & Co																
Sherman Laboratories																
Smith-Dorsey, a division of The																
Spirt & Co., Inc.	f1		. 01		1		*		. 50	. 52			74		0.07	
E. R. Squibb & Sons, Division of M	ath	1eso1	n Cin	em	icai	Coi	rp.	. 6	5, 52	-53	, 00	-01	, /1	, 00-0	9, 91,	112, 110
The Upjohn Company		٠	*	*						*,				Insert I	acing	Page 32
Varick Pharmacal Company, Inc																
Wallace Laboratories																
Warner-Chilcott Laboratories .																
Winthrop Laboratories																
Wyeth Laboratories					*										. 13	5, 31, 67





### should a non-diabetic, transient glycosuria ever be considered unimportant?

Never. A patient showing even a mild transient glycosuria should be observed for years as a diabetic suspect.\*

Ultimate diagnosis on 126 patients with a previous transient mild glycosuria. Twenty diabetics were discovered 5-10 years after a recorded glycosuria—10 diabetics after more than 10 years.\*

\*Murphy, R.: Connecticut M. J. 21:306, 1957.

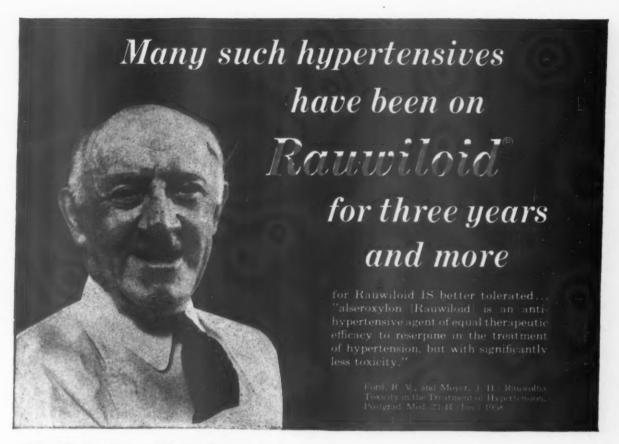
### COLOR CALIBRATED CLINITEST® Reagent Tablets

the STANDARDIZED urine-sugar test for reliable quantitative estimations

- full color calibration, clear-cut color changes
- established "plus" system covers entire critical range
- standard blue-to-orange spectrum long familiar to diabetics
- unvarying, laboratory-controlled color scale



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No Tolerance Development **Lower Incidence of Depression** 



For gratifying Rauwolfia response virtually free from side actions

When more potent drugs are needed, prescribe



Rauwiloid® + Veriloid®

for moderate to severe hypertension. Initial dose 1 tablet t.i.d., p.c.

Rauwiloide and he Herramathonium 250 mg. in severe, otherwise intractable hypertension. Initial dose 1/2 tablet q.i.d.

Both combinations in convenient single-tablet form.

# UNIQUE

in the treatment of severe hypertension

# BECAUSE

it increases renal blood flow



Inherent as a basic problem of severe hypertension is renal ischemia. Even though they reduce blood pressure to

varying degrees, antihypertensive agents may often diminish renal blood flow.

Apresoline not only lowers blood pressure but increases renal blood flow and cardiac output, producing a "most striking improvement in cardiovascular and renal function . . . "\*

\*Judson, W. E., Hollander, W., and Wilkins, R. W.: Circulation 13:664 (May) 1956.

**Apresoline** 

(hydralazine hydrochloride CIBA)

Ampuls, 1 ml., 20 mg. per ml.
Tablets, 10 mg. (yellow,
double-scored), 25 mg. (blue,
coated), 50 mg. (pink, coated);
bottles of 100, 500 and 1000.
Tablets, 100 mg. (orange, coated);
bottles of 100 and 1000.

CIBA